Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

0 F

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21 **EXPEDIENTE No** 07-15793

54 **TÍTULO** INHIBIDORES DE LA ARN POLIMERASA DEPENDIENTE DE ARN DEL VIRUS DE LA HEPATITIS C Y COMPOSICIONES Y TRATAMIENTO QUE LOS USAN

51 **CLASIFICACIÓN INTERNACIONAL** A61K31/357 // A61K31/366 A61P31/14

71 **SOLICITANTE** PFIZER INC.

78-03-2007 ubicacion

DOMICILIO 235 East 42nd Street, New York, NY 10017 EUA

74 **APODERADO** CARLOS OLARTE

22 **BOGOTÁ, D C,** 16 DE FEBRERO, 2007

(FORMA P 10)

55

07/17

OlarteRaisbeck

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 07-015793- -00000-0000
Fec: 2007-02-16 16:55:22 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEIYII
Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 715

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

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

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: PFIZER INC
Dirección: 235 East 42nd Street, New York, NY 10017 E.U.A.
Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: Delaware, Estados Unidos de América.
Teléfono: _____ **Fax:** _____
E-mail: _____

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

(3) **REPRESENTANTE APODERADO**

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número 79.782.747Bta
TP 74.295

(4) **INVENTOR (ES) (72)**

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

(5) **PCT (86)**
Solicitud Internacional No. PCT/IB2005/002697 Fecha Agosto 5, 2005
Publicación Internacional No. WO 2006/018725 Fecha Febrero 23,2006

(6) **Título (54)** INHIBIDORES DE LA ARN POLIMERASA DEPENDIENTE DE ARN DEL VIRUS DE LA HEPATITIS C Y COMPOSICIONES Y TRATAMIENTO QUE LOS USAN

Clasificación Internacional (51) C07D 487/04; 405/06; 309/32; 513/04; 405/14; A61K 31/351; 31/366; A61P 31/14

Prioridad
SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Agosto 18, 2004	60/602.618

(9) **Comprobante de pago No.** 07-13.366 **Fecha** Febrero 13, 2007

(0) **ANEX S**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Ver Expediente 06-051.757. Adjunto Copia Simple
- [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).
- [x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [x] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(1) **FIGURA CARACTERÍSTICA:**

(2) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

LISTA DE INVENTORES PCT/IB2005/002697

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4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 07-015793- -00000-0000
Fec. 2007-02-15 15:35:22 Dep. 2020 NUECREACIONES
Tra 11 PATENTEIYII
Eve: 379 FASENACIONALII
Act 411 PRESENTACION Folios: 716

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 13,366
FECHA : FEBRERO 13 DE 2007

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
OLARTE RAISBECK	CONSIGNACION	BANCO POPULAR	050-00116-6	57477376	13/02/2007	1,446,000.00

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	482,000.00
		TOTAL : $	482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

5

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

PFIZER INC.

Bilingüe inglés- español otorgado en Nueva York, Estados Unidos el 14 de julio de 2003 y firmado por J. Trevor Lumb, Vicepresidente de Pfizer Products Inc.

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 14 de julio de 2003 el suscrito notario Kenneth Greenwood certifica que J. Trevor Lumb, domiciliado en Nueva York ejercía funciones de Asistente General Consejero de Patentes la Compañía Pfizer Inc., con sede en Nueva York, Nueva York, Estados Unidos.

Firma del notario: Kenneth Greenwood

Sello notarial: certificado, verificado y autenticado en la Localidad de Egham en Surrey, 14 julio, 2003 por el Notario Kenneth Greenwood-Horne Engall & Freeman

Sello Notario Público en alto relieve rojo.

APOSTILLA

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País :Reino Unido de Gran Bretaña e Irlanda del Norte
   Este documento Público
2. ha sido firmado por K. Greenwood
3. ejerce funciones de Notario Público
4. Lleva el sello de dicho Notario Público

CERTIFICADÓ

5. En Londres 6. El 17 de julio de 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
8. No. G210434
9. Sello del Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
10. Firma de R. Bawden - Por Secretario de Estado

Si el documento se usa en un país que no es parte de la convención de la Haya del 5 de octubre 1961, debe presentarse en sección consular de la misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 25 de julio-2003. Marlen Neira C.

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1997

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned,

Pfizer Inc.

domiciled in

235 East 42nd Street, New York, NY 10017 USA

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs 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, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

Pfizer Inc.

domiciliado en

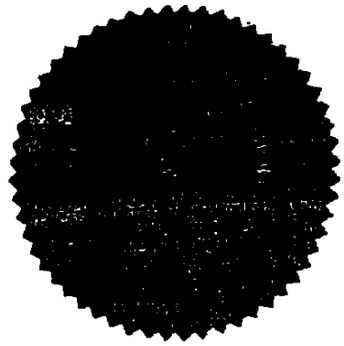
235 East 42nd Street, New York, NY 10017 USA

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales 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, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir 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: _____

Date/Fecha: July 14, 2003

City,Country/Ciudad,País: New York, USA



OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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FAX: +57-1 638-6201

www.olarteraisbeck.com

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Notarial Certification

On this date,
July 14, 2003
The undersigned Notary Public certifies:

1. That J. Trevor Lumb
of legal age and domiciled in New York, USA
signed the foregoing document.

2. That the grantor has executed the foregoing document as Assistant General Patent Counsel of Pfizer Inc.

3. That Pfizer Inc.,
having its principal place of business located in New York, New York, U.S.A.
is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

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

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

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que
J. Trevor Lumb
mayor de edad y domiciliado
New York
suscribió el documento que antecede.

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

4. Que
con sede principal ubicada en

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

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

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

NOTARY PUBLIC (Signature):

EXECUTION
Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 14th Day Of July 2003
KENNETH GARENWOOD
NOTARY PUBLIC
HOWNE ENGALL AND FREEMAN

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by K Greenwood
a été signé par

3. Acting in the capacity of Notary Public
agissant en qualité de

4. Bears the seal/stamp of The Said Notary Public
est revêtu du sceau/timbre de

Certified/Attesté

5. at London/à Londres 6. the/le 17 July 2003

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No G210434

9. Stamp:
timbre:

10. Signature: R. Bawden

FOREIGN AND COMMONWEALTH OFFICE LONDON

* For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country.

Sépase que Yo, GEORGE ANDREW LEWIS, de Westminster House 35 Windsor Road Slough Berkshire Reino Unido un Notario Público debidamente autorizado.

CERTIFICO QUE EL DOCUMENTO ANEXADO AL PRESENTE LLAMADO:

CESION, firmada por Javier GONZALEZ, Tanya Michelle JEWELL, Hui LI, Angelica LINTON, John Howard TATLOCK.

Ha sido presentado ante mi por los Servicios Consulares de Blair en nombre de Pfizer con base en un documento original con firmas debidamente autenticas.

Firmado y sellado en 35 Windsor Road según lo dicho anteriormente, el 17 de enero de 2007.

[Firmado y sellado]

GEORGE ANDREW LEWIS
Notario Público

APOSTILLA

(Convención de La Haya del 5 de octubre de 1961)

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
2. Este documento público ha sido firmado por: George Andrew Lewis
3. obrando en su condición de Notario Público
4. lleva el sello/estampilla de dicho Notario Público

Certificado

5. en Londres
6. el 18 de enero de 2007
7. por: Secretario Principal de Estado de su Majestad para Asuntos Extranjeros
8. No. H260475
9. Sello / Estampilla
   [Sellado]
10. Firma: N. Donkor
    [Firmado]

PC32310A
CO-1X

CESIÓN

A cambio de una contraprestación de valor, la cual me (nos) pagó **PFIZER INC.**, una sociedad constituida y existente bajo las leyes del Estado de Delaware, Estados Unidos de América, de 235 East 42nd Street, New York, New York 10017, Estados Unidos de América, por el presente le vendo y le cedo (le vendemos y le cedemos) a la citada **PFIZER INC.** la totalidad de mis (nuestros) derechos, el título y el interés que tengo (tenemos) en mi (nuestro) invento de una cierta mejora, nueva y útil, de **INHIBIDORES DE LA ARN POLIMERASA DEPENDIENTE DE ARN DEL VIRUS DE LA HEPATITIS C Y C MPOSICIONES Y TRATAMIENTO QUE LOS USAN,** en la medida en que esta cesión concierna a la República de Colombia, tal y como se describe plenamente el mismo en las especificaciones, y yo (nosotros) autorizo (autorizamos) y le solicito (solicitamos) por el presente a la Oficina de Patentes de Colombia que le expida dicha patente a la citada **PFIZER INC.,** de conformidad con la presente cesión.

En fe de lo cual firmamos con mi puño y letra el día de hoy.

(Firmado) 7 de Julio de 2005 Javier GONZALEZ
San Diego, California (USA)- Javier GONZALEZ

(Firmado) 7 de Julio de 2005 Tanya Michelle JEWELL
San Diego, California (USA)- Tanya Michelle JEWELL

(Firmado) 7 de Julio de 2005 Hui LI
San Diego, California (USA)- Hui LI

(Firmado) 7 de Julio de 2005 Angélica LINTON

San Diego, California (USA)- Angélica LINTON

(Firmado) 7 de Julio de 2005 John Howard TATLOCK

San Diego, California (USA)- John Howard TATLOCK

BE IT KNOWN that I, GEORGE ANDREW LEWIS of Westminster House 35 Windsor Road Slough Berkshire United Kingdom a duly authorised Notary Public

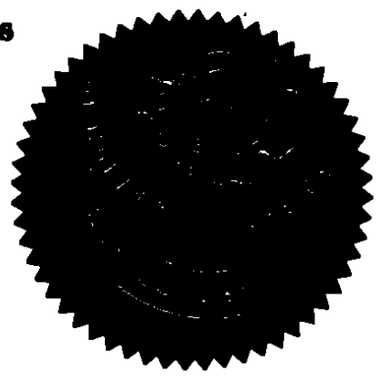
CERTIFY that the document annexed hereto, namely:

ASSIGNMENT, Signed by Javier GONZALEZ, Tanya Michelle JEWELL, Hui LI, Angelica LINTON and John Howard TATLOCK

has been presented before me by Blair Consular Services on behalf of Pfizer on the basis that it is an authentic duly signed original document

SIGNED and sealed at 35 Windsor Road aforesaid on 17th January 2007.

George Andrew Lewis
Notary Public



13

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by — George Andrew Lewis
   a été signé par

3. Acting in the capacity of — Notary Public
   agissant en qualité de

4. Bears the seal/stamp of — The Said Notary Public
   est revêtu du sceau/timbre de

Certified/Attesté

5. at London/à Londres

6. the/le 18 January 2007

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
   par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **H260475**

9. Stamp:
   timbre:

10. Signature: N. Donker

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.

PC32310A

CO-1

ASSIGNMENT

For valuable consideration paid to me (us) by **PFIZER INC.** a corporation organized under the laws of the State of Delaware, United States of America whose full post office address is 235 East 42nd Street, New York, New York 10017, United States of America, I (we) do hereby sell and assign to the said **PFIZER INC.**, all my (our) right, title and interest in and to my (our) invention for a new and useful Improvement in **INHIBITORS OF THE HEPATITIS C VIRUS RNA-DEPENDENT RNA POLYMERASE, AND COMPOSITIONS AND TREATMENTS USING THE SAME** so far as the Republic of Colombia is concerned, as fully set forth and described in the specification, and I (we) do hereby authorize and request the Commissioner of Patents of Colombia to issue said patent to the said **PFIZER INC.** in accordance with this assignment.

In witness whereof I (we) have hereunto set my (our) hand(s) this

July 7 2005
San Diego,California(USA) on / /2005 - Javier GONZALEZ

July 7, 2005 Tanya Jewell
San Diego,California(USA) on / /2005 - Tanya Michelle JEWELL

July 7, 2005
San Diego,California(USA) on / /2005 - Hui LI

July 7, 2005
San Diego,California(USA) on / /2005 - Angelica LINTON

July 7, 2005
San Diego,California(USA) on / /2005 - John Howard TATLOCK

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

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
23 February 2006 (23.02.2006)

(10) International Publication Number
WO 2006/018725 A1

(51) International Patent Classification[7]: C07D 487/04, 405/06, 309/32, 513/04, 405/14, A61K 31/351, 31/366, A61P 31/14

(21) International Application Number: PCT/IB2005/002697

(22) International Filing Date: 5 August 2005 (05.08.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/602,618 18 August 2004 (18.08.2004) US

(71) Applicant (*for all designated States except US*): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): GONZALEZ, Javier [US/US]; Patent Department, Agouron/Pfizer La Jolla, 10777 Science Center Drive, San Diego, CA 92121 (US). JEWELL, Tanya, Michelle [US/US]; Patent Department, Agouron/Pfizer La Jolla, 10777 Science Center Drive, San Diego, CA 92121 (US). LI, Hui [US/US]; Patent Department, Agouron/Pfizer La Jolla, 10777 Science Center Drive, San Diego, CA 92121 (US). LINTON, Angelica [US/US]; Patent Department, Agouron/Pfizer La Jolla, 10777 Science Center Drive, San Diego, CA 92121 (US). TATLOCK, John, Howard [US/US]; Patent Department, Agouron/Pfizer La Jolla, 10777 Science Center Drive, San Diego, CA 92121 (US).

(74) Agent: RUDDOCK, Keith, S.; c/o Pfizer Research and Development, Ramsgate Road, Kent, Sandwich CT13 9NJ (GB).

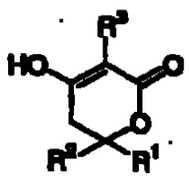
(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, 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, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publication:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INHIBITORS OF HEPATITIS C VIRUS RNA-DEPENDENT RNA POLYMERASE, AND COMPOSITIONS AND TREATMENTS USING THE SAME



(4)

(57) Abstract: The present invention provides compounds of formula (4), and their pharmaceutically acceptable salts and solvates, which are useful as inhibitors of the Hepatitis C virus (HCV) polymerase enzyme and are also useful for the treatment of HCV infections in HCV-infected mammals. The present invention also provides pharmaceutical compositions comprising compounds of formula (4), their pharmaceutically acceptable salts and solvates. Furthermore, the present invention provides intermediate compounds and methods useful in the preparation of compounds of formula (4).

WO 2006/018725 A1

INHIBITORS OF HEPATITIS C VIRUS RNA-DEPENDENT RNA POLYMERASE, AND COMPOSITIONS AND TREATMENTS USING THE SAME

Field of the Invention

The present invention relates to compounds useful as inhibitors of the Hepatitis C virus (HCV) polymerase enzyme, pharmaceutical compositions comprising such compounds, methods of using such compounds and formulations in the treatment of HCV-infected mammals, such as humans, and methods and intermediates compounds useful in preparing such compounds.

Background

The invention relates to agents that inhibit hepatitis C virus (HCV) RNA-dependent RNA polymerase (RdRp). The invention also relates to the use of such compounds in pharmaceutical compositions and therapeutic treatments useful for inhibition of HCV replication.

HCV is an enveloped RNA virus containing a single-stranded positive-sense RNA genome approximately 9.5 kb in length (Choo, et al., *Science* 244:359-362 (1989)). The RNA genome contains a 5'-nontranslated region (5' NTR) of 341 nucleotides (Brown, et al., *Nucl. Acids Res.* 20:5041-5045 (1992); Bukh, et al., *Proc. Natl. Acad. Sci. USA* 89:4942-4946 (1992)), a large open reading frame (ORF) encoding a single polypeptide of 3,010 to 3,040 amino acids (Choo, et al. (1989), *supra*), and a 3'-nontranslated region (3'-NTR) of variable length of about 230 nucleotides (Kolykhalov, et al., *J. Virol.* 70:3363-3371 (1996); Tanaka, et al., *J. Virol.* 70:3307-3312 (1996)).

The 5' NTR is one of the most conserved regions of the viral genome and plays a pivotal role in the initiation of translation of the viral polyprotein. A single ORF encodes a polyprotein that is co- or post-translationally processed into structural (core, E1, and E2) and nonstructural (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) viral proteins by either cellular or viral proteinases (Bartenschlager (1997), *supra*). The 3' NTR consists of three distinct regions: a variable region of about 38 nucleotides following the stop codon of the polyprotein, a polyuridine tract of variable length with interspersed substitutions of cytosine, and 98 nucleotides (nt) at the very 3' end which are highly conserved among various HCV isolates. The order of the genes within the genome is: NH_2-C-E1-E2-p7-NS2-NS3-NS4A-NS4B-NS5A-NS5B-COOH (Grakoui, et al., *J. Virol.* 67:1385-1395 (1993)).

Hepatitis C virus (HCV) is a member of the hepacivirus genus in the family *Flaviviridae*. It is the major causative agent of non-A, non-B viral hepatitis and is the major cause of transfusion-associated hepatitis and accounts for a significant proportion of hepatitis cases worldwide. Although acute HCV infection is often asymptomatic, nearly 80% of cases

resolve to chronic hepatitis. The persistent property of the HCV infection has been explained by its ability to escape from the host immune surveillance through hypermutability of the exposed regions in the envelope protein E2 (Weiner, et al., *Virology* 180:842-848 (1991); Weiner, et al. *Proc. Natl. Acad. Sci. USA* 89:3468-3472 (1992).

Processing of the structural proteins core (C), envelope protein 1 and (E1, E2), and the p7 region is mediated by host signal peptidases. In contrast, maturation of the nonstructural (NS) region is accomplished by two viral enzymes. The HCV polyprotein is first cleaved by a host signal peptidase generating the structural proteins C/E1, E1/E2, E2/p7, and p7/NS2 (Hijikata, et al., *Proc. Natl. Acad. Sci. USA* 88:5547-5551 (1991); Lin, et al., *J. Virol.* 68:5063-5073 (1994)). The NS2-3 proteinase, which is a metalloprotease, then cleaves at the NS2/NS3 junction. The NS3/4A proteinase complex (NS3 serine protease/NS4A cofactor), then at all the remaining cleavage sites (Bartenschlager, et al., *J. Virol.* 67:3835-3844 (1993); Bartenschlager, (1997), *supra*). RNA helicase and NTPase activities have also been identified in the NS3 protein. The N-terminal one-third of the NS3 protein functions as a protease, and the remaining two-thirds of the molecule acts as a helicase/ATPase, which is thought to be involved in HCV replication (Bartenschlager, (1997), *supra*). NS5A may be phosphorylated and act as a putative cofactor of NS5B. The fourth viral enzyme, NS5B, is an RNA-dependent RNA polymerase (RdRp) and a key component responsible for replication of the viral RNA genome (Lohmann, et al., *J. Virol.* 71:8416-8428 (1997)).

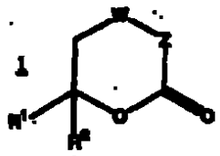
Replication of HCV is thought to occur in membrane-associated replication complexes. Within these, the genomic plus-strand RNA is transcribed into minus-strand RNA, which in turn can be used as a template for synthesis of progeny genomic plus strands. Two viral proteins appear to be involved in this reaction: the NS3 protein, which carries in the carboxy terminal two-thirds a nucleoside triphosphatase/ RNA helicase, and the NS5B protein, which is a membrane-associated phosphoprotein with an RNA-dependent RNA polymerase activity (RdRp) (Hwang, et al., *J. Virol.* 227:439-446 (1997)). While the role of NS3 in RNA replication is less clear, NS5B apparently is the key enzyme responsible for synthesis of progeny RNA strands. Using recombinant baculoviruses to express NS5B in insect cells and a synthetic nonviral RNA as a substrate, two enzymatic activities have been identified as being associated with NS5B. The two activities include a primer-dependent RdRp and a terminal transferase (TNTase) activity. NS5B's activity was confirmed and further characterized through the use of the HCV RNA genome as a substrate (Lohmann, et al., *Virology* 249:108-118 (1998)). Recent studies have shown that NS5B with a C-terminal 21 amino-acid truncation expressed in *Escherichia coli* is also active for *in vitro* RNA synthesis

(Ferrari, et al., *J. Virol.* 73:1649-1654 (1999); Yamashita, et al., *J. Biol. Chem.* 273:15479-15486 (1998)).

Since persistent infection of HCV is related to chronic hepatitis and eventually to hepatocarcinogenesis, HCV replication is one of the targets to eliminate HCV reproduction and to prevent hepatocellular carcinoma. Unfortunately, present treatment approaches for HCV infection are characterized by relatively poor efficacy and an unfavorable side-effect profile. Therefore, intensive effort is directed at the discovery of molecules to treat this disease, including the discovery of drugs designed to inhibit HC replication, as there is a persistent need for non-peptide, small-molecule compounds that are HCV RdRp inhibitors having desirable or improved physical and chemical properties appropriate for pharmaceutical applications.

SUMMARY OF THE INVENTION

The present invention relates to compounds of the formula I



and to pharmaceutically acceptable salts, hydrates, metabolites, prodrugs and solvates thereof, wherein:

W-Z is -C(=O)-C(-R^3)(H)- or -C(-OR^6)=C(-R^3)-, wherein when W-Z is –C(-OR^6)=C(-R^3)-;

each R^1 is independently selected from hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, (C_3-C_{10}) cycloalkyl, 4- to 10-membered heterocyclic, and C_6-C_{10} aryl, wherein the foregoing R^1 groups, except H, are optionally substituted by 1 to 4 substituents selected from R^4;

R^2 is selected from the group of R^1 substituents, -(CR^5R^5)$_q$(C_6-C_{10} aryl), -(CR^5R^5)$_q$(4-10 membered heterocyclic), -(CR^5R^5)$_q$C(O)(CR^5R^5)$_t$(C_6-C_{10} aryl), -(CR^5R^5)$_q$C(O)(CR^5R^5)$_t$(4-10 membered heterocyclic), -(CR^5R^5)$_q$O(CR^5R^5)$_t$(C_6-C_{10} aryl), -(CR^5R^5)$_q$O(CR^5R^5)$_t$(4-10 membered heterocyclic), -(CR^5R^5)$_q$SO$_n$(CR^5R^5)$_t$(C_6-C_{10} aryl), and -(CR^5R^5)$_q$SO$_n$(CR^5R^5)$_t$(4-10 membered heterocyclic), wherein q and t are each independently an integer from 0 to 5, n is an integer from 0 to 2, the alkyl, aryl and heterocyclic moieties of said R^2 groups are optionally substituted by 1 to 5 R^4 groups, and with the proviso that R^2 is not H;

R^3 is hydrogen, -OR^6, -SR^6, -NR^6R^7, and the group of R^2 substituents;

R^7 is selected from the group of R^2 substituents except R^7 is not H;

each R^4 is independently selected from halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, C_1-C_{10} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)NR^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-NR^6OR^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, $-(CR^8R^9)_t(C_6$-C_{10} aryl)(wherein t is an integer from 0 to 5), $-(CR^8R^9)_t$(4-10 membered heterocyclic)(wherein t is an integer from 0 to 5); C_3-C_{10} cycloalkyl, R^6-O-, R^6-SO_n- (wherein n is an integer from 0 to 2), and oxo (=O), and wherein the alkyl, aryl, and heterocyclic moieties of said R^4 groups are optionally substituted by 1 to 4 substituents selected from R^5;

each R^5 is independently selected from halo, trifluoromethyl, trifluoromethoxy, cyano, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-OR^6$, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, 4- to 10-membered heterocyclic, oxo (=O), $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^6$, $-NR^6C(O)NR^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-NR^6OR^7$, $-NR^6SO_2R^7$ and $-SO_2NR^6R^7$, wherein the alkyl, aryl and heterocyclic moieties of the foregoing R^5 groups are optionally substituted by 1 to 3 R^{10};

each R^6 and R^7 is independently selected from H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, $-(CR^8R^9)_t(C_6$-C_{10} aryl), and $-(CR^8R^9)_t$(4-10 membered heterocyclic), wherein t is an integer from 0 to 5, 1 or 2 ring carbon atoms of the heterocyclic group are optionally substituted with an oxo (=O) moiety, and the alkyl, aryl and heterocyclic moieties of the foregoing R^6 and R^7 groups are optionally substituted with 1 to 3 halo, cyano, trifluoromethyl, trifluoromethoxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-(CR^8R^9)_t(C_6$-C_{10} aryl), and $-(CR^8R^9)_t$(4-10 membered heterocyclic), wherein t is an integer from 0 to 5;

each R^8 and R^9 is independently selected from H and C_1-C_4 alkyl; and

each R^{10} is independently selected from halo, cyano, trifluoromethyl, trifluoromethoxy, $-C(O)O$-R^6, $-OR^6$, $-C(O)(CR^8R^9)_pC(O)OR^6$, wherein p is an integer from 1 to 5, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, and $-NR^6R^7$.

The present invention also relates to compounds of formula (1), wherein:

W-Z is $-C(=O)$-$C(-R^5)(H)$- or $-C(-OR^5)=C(-R^5)$-;

each R^1 is independently selected from hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, (C_3-C_{10})-cycloalkyl, (4- to 10-membered heterocyclic, and C_6-C_{10} aryl, wherein the foregoing R^1 groups, except H, are optionally substituted by 1 to 4 substituents selected from R^4;

R^5 is selected from the group of R^1 substituents, $-(CR^8R^9)_t(C_3$-C_{10} cycloalkyl), $-(CR^8R^9)_t(C_6$-C_{10} aryl), $-(CR^8R^9)_t$(4-10 membered heterocyclic), $-(CR^8R^9)_tC(O)(CR^8R^9)_t(C_6$-$C_{10}$ aryl), $-(CR^8R^9)_tC(O)(CR^8R^9)_t$(4-10 membered heterocyclic), $-(CR^8R^9)_tO(CR^8R^9)_t(C_6$-$C_{10}$ aryl), $-(CR^8R^9)_tO(CR^8R^9)_t$(4-10 membered heterocyclic), $-(CR^8R^9)_tSO_n(CR^8R^9)_t(C_6$-$C_{10}$ aryl), and

$-(CR^5R^5)_qSO_n(CR^5R^5)_t$(4-10 membered heterocyclic), wherein q and t are each independently an integer from 0 to 5, n is an integer from 0 to 2, the alkyl, cycloalkyl, aryl and heterocyclic moieties of said R^6 groups are optionally substituted by 1 to 5 R^4 groups, and with the proviso that R^6 is not H;

R^3 is hydrogen, $-OR^6$, $-SR^6$, $-NR^6R^7$, and the group of R^6 substituents;

R^7 is selected from the group of R^6 substituents;

each R^4 is independently selected from halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, C_1-C_{10} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_{10} cycloalkyl, $-(CR^5R^5)_tN(R^5)_2$, $-(CR^5R^5)_tNR^5C(O)R^6$, $-(CR^5R^5)_tOR^6$, $-(CR^5R^5)_tC(O)R^6$, $-(CR^5R^5)_tC(O)OR^6$, $-(CR^5R^5)_tC(O)R^6$, $-(CR^5R^5)_tNR^5C(O)R^7$, $-(CR^5R^5)_tNR^5C(O)OR^6$ $-(CR^5R^5)_tNR^5C(O)NR^7$, $-(CR^5R^5)_tC(O)NR^6R^7$, $-(CR^5R^5)_tNR^6R^7$, $-(CR^5R^5)_tNR^6OR^7$, $-(CR^5R^5)_tSO_2NR^6R^7$, $-(CR^5R^5)_tNR^5SO_2R^7$, $-(CR^5R^5)_t(C_6$-C_{10} aryl)(wherein t is an integer from 0 to 5), $-(CR^5R^5)_t$(4-10 membered heterocyclic)(wherein t is an integer from 0 to 5), C_3-C_{10} cycloalkyl, R^5-O-, R^5-SO_n-$(CR^5R^5)_r$- (wherein n is an integer from 0 to 2), and oxo (=O), and wherein the alkyl, aryl, and heterocyclic moieties of said R^4 groups are optionally substituted by 1 to 4 substituents selected from R^5;

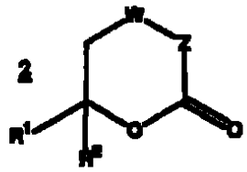
each R^5 is independently selected from halo, trifluoromethyl, trifluoromethoxy, cyano, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-OR^6$, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, 4- to 10-membered heterocyclic, oxo (=O), $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^6$, $-NR^6C(O)NR^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-NR^6OR^7$, $-NR^6SO_2R^7$ and $-SO_2NR^6R^7$, wherein the alkyl, aryl and heterocyclic moieties of the foregoing R^5 groups are optionally substituted by 1 to 3 R^{10};

each R^6 and R^7 is independently selected from H, cyano, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, $-(CR^5R^5)_t(C_6$-C_{10} aryl), and $-(CR^5R^5)_t$(4-10 membered heterocyclic), $-(CR^5R^5)_tC(O)R^6$ wherein t is an integer from 0 to 5, 1 or 2 ring carbon atoms of the heterocyclic group are optionally substituted with an oxo (=O) moiety, and the alkyl, aryl and heterocyclic moieties of the foregoing R^6 and R^7 groups are optionally substituted with 1 to 3 halo, cyano, C_3-C_{10} cycloalkyl, $-C(O)OR^5$, $-NR^5C(O)R^5$, $-(CR^5R^5)_tNR^5R^5$, $-OR^5$, $-NC(O)R^5$, trifluoromethyl, trifluoromethoxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-(CR^5R^5)_t(C_6$-C_{10} aryl), and $-(CR^5R^5)_t$(4-10 membered heterocyclic), wherein t is an integer from 0 to 5;

each R^8 and R^9 is independently selected from H and C_1-C_6 alkyl; and

each R^{10} is independently selected from halo, cyano, trifluoromethyl, trifluoromethoxy, $-C(O)OR^5$, $-C(O)O-R^5$, $-OR^5$, $-C(O)(CR^5R^5)_pC(O)OR^5$, wherein p is an integer from 1 to 5, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, and $-NR^5R^7$.

The present futher relates to a comound of the formula 2



and pharmaceutically acceptable salts, solvates, metabolites, prodrugs and solvates thereof, wherein:

W-Z is $-C(-OR^6)=C(-R^5)-$;

R^1 is cyclopentyl;

R^2 is $-(CR^8R^8)_t(C_6-C_{10}$ aryl) or $-(CR^8R^8)_t$(4-10 membered heterocyclic), wherein t is an integer from 0 to 5, and the aryl and heterocyclic moieties of said R^2 groups are optionally substituted by 1 to 5 R^4 groups, and with the proviso that R^2 is not H;

R^3 is hydrogen, $-OR^6$, $-SR^6$, $-NR^6R^7$, and the group of R^2 substituents;

each R^4 is independently selected from halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, C_1-C_{10} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)NR^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-NR^6OR^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, $-(CR^8R^8)_t(C_6-C_{10}$ aryl)(wherein t is an integer from 0 to 5), $-(CR^8R^8)_t$(4-10 membered heterocyclic)(wherein t is an integer from 0 to 5), C_3-C_{10} cycloalkyl, R^6-O-, R^6-SO_n- (wherein n is an integer from 0 to 2), and oxo (=O), and wherein the alkyl, aryl, and heterocyclic moieties of said R^4 groups are optionally substituted by 1 to 4 substituents selected from R^5;

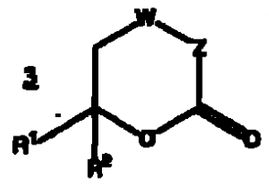
each R^5 is independently selected from halo, trifluoromethyl, trifluoromethoxy, cyano, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-OR^6$, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, 4- to 10-membered heterocyclic, oxo (=O), $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^6$, $-NR^6C(O)NR^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-NR^6OR^7$, $-NR^6SO_2R^7$ and $-SO_2NR^6R^7$, wherein the alkyl, aryl and heterocyclic moieties of the foregoing R^5 groups are optionally substituted by 1 to 3 R^{10};

each R^6 and R^7 is independently selected from H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, $-(CR^8R^8)_t(C_6-C_{10}$ aryl), and $-(CR^8R^8)_t$(4-10 membered heterocyclic), wherein t is an integer from 0 to 5, 1 or 2 ring carbon atoms of the heterocyclic group are optionally substituted with an oxo (=O) moiety, and the alkyl, aryl and heterocyclic moieties of the foregoing R^6 and R^7 groups are optionally substituted with 1 to 3 halo, cyano, trifluoromethyl, trifluoromethoxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $(CR^8R^8)_t(C_6-C_{10}$ aryl), and $-(CR^8R^8)_t$(4-10 membered heterocyclic), wherein t is an integer from 0 to 5;

each R^8 and R^9 is independently selected from H and C_1-C_4 alkyl; and

each R^{10} is independently selected from halo, cyano, trifluoromethyl, trifluoromethoxy, $-C(O)O-R^6$, $-OR^6$, $-C(O)(CR^8R^8)_pC(O)OR^6$, wherein p is an integer from 1 to 5, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, and NR^6R^7.

The present invention further relates to a compound of the formula (3)



and to pharmaceutically acceptable salts, solvates, prodrugs, and metabolites thereof, wherein:

W-Z is $-C(=O)-C(-R^5)(H)-$;

R^1 is cyclopentyl;

R^2 is $-(CR^8R^8)_t(C_6$-C_{10} aryl) or $-(CR^8R^8)_t$(4-10 membered heterocyclic), wherein t is an integer from 0 to 5, and the aryl and heterocyclo moieties of said R^2 groups are optionally substituted by 1 to 5 R^4 groups, and with the proviso that R^2 is not H;

R^5 is hydrogen;

each R^4 is independently selected from halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, C_1-C_{10} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)NR^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-NR^6OR^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, $-(CR^8R^8)_t(C_6$-C_{10} aryl)(wherein t is an integer from 0 to 5), $-(CR^8R^8)_t$(4-10 membered heterocyclic)(wherein t is an integer from 0 to 5), C_3-C_{10} cycloalkyl, R^6-O-, R^6-SO_n- (wherein n is an integer from 0 to 2), and oxo (=O), and wherein the alkyl, aryl, and heterocyclic moieties of said R^4 groups are optionally substituted by 1 to 4 substituents selected from R^5;

each R^5 is independently selected from halo, trifluoromethyl, trifluoromethoxy, cyano, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-OR^6$, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, 4- to 10-membered heterocyclic, oxo (=O), $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^6$, $-NR^6C(O)NR^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-NR^6OR^7$, $-NR^6SO_2R^7$ and $-SO_2NR^6R^7$, wherein the alkyl, aryl and heterocyclic moieties of the foregoing R^5 groups are optionally substituted by 1 to 3 R^{10};

each R^6 and R^7 is independently selected from H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, $-(CR^8R^8)_t(C_6$-C_{10} aryl), and $-(CR^8R^8)_t$(4-10 membered heterocyclic), wherein t is an integer from 0 to 5, 1 or 2 ring carbon atoms of the heterocyclic group are optionally substituted with an oxo (=O) moiety, and the alkyl, aryl and heterocyclic moieties of the foregoing R^6 and R^7

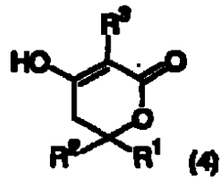
groups are optionally substituted with 1 to 3 halo, cyano, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $(CR^8R^8)_t(C_6$-C_{10} aryl), and -$(CR^8R^8)_t$(4-10 membered heterocyclic), wherein t is an integer from 0 to 5;

each R^8 and R^9 is independently selected from H and C_1-C_6 alkyl; and

each R^{10} is independently selected from halo, cyano, trifluoromethyl, trifluoromethoxy, -C(O)O-R^8, -OR^8, -C(O)$(CR^8R^8)_pC(O)OR^8$, wherein p is an integer from 1 to 5, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, and NR^8R^7.

In a specific embodiment of the present invention, according to formula 1, R^2 is -$(CR^8R^8)_t(C_6$-C_{10} aryl), wherein t is an integer from 2 to 5, and the aryl moiety of said R^2 group is optionally substituted by 1 to 5 R^4 groups, and with the proviso that R^2 is not H; optionally each R^4 is independently selected from halo, nitro, C_1-C_{10} alkyl, -C(O)R^6, -C(O)OR^6, -OC(O)R^6, -C(O)NR^6R^7, -$(CR^8R^8)_t$(4-10 membered heterocyclic)(wherein t is an integer from 0 to 5), C_3-C_{10} cycloalkyl, R^6-O-, and wherein the alkyl, aryl, and heterocyclic moieties of said R^4 groups are optionally substituted by 1 to 4 substituents selected from R5, optionally each R^5 is independently selected from halo, trifluoromethyl, C_1-C_6 alkyl, -OR^6, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, oxo (=O), -C(O)R^6, -C(O)OR^6, -OC(O)R^6, -NR^6C(O)R^6, -NR^6C(O)NR^7, -C(O)NR^6R^7, -NR^6R^7, -NR^6OR^7, -$NR^6SO_2R^7$ and -$SO_2NR^6R^7$, wherein the alkyl and aryl moieties of the foregoing R^5 groups are optionally substituted by 1 to 3 R^{10}; optionally each R^{10} is independently selected from halo, trifluoromethyl, -C(O)O-R^8, -OR^8, C_1-C_6 alkyl and NR^8R^7; optionally R^2 is -OR^8, -SR^8, -NR^8R^7, and -$(CR^8R^8)_t(C_6$-C_{10} aryl), wherein t is an integer from 2 to 5, and the aryl moiety of said R^2 group is optionally substituted by 1 to 5 R^4 groups.

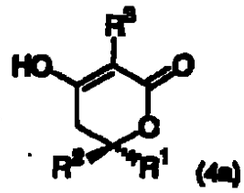
In another aspect of the present invention are provided compounds of formula (4),



(4)

wherein any of the definitions of R^1, R^6 and R^2 below apply.

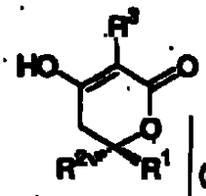
Also provided are compounds of formula (4a),



(4a)

wherein any of the definitions of R^1, R^2 and R^3 below apply.

Further provided are compounds of formula (4b),



(4b)

wherein any of the definitions of R^1, R^2 and R^3 below apply.

It is specifically contemplated herein that compounds of formula (4) are meant to encompass both compounds of formulae (4a) and (4b), unless otherwise indicated.

In a further aspect are provided compounds of formula (4) wherein:

R^1 is cyclopentyl;

R^2 is $-(CR^6R^7)_n$(5-6 membered heterocyclic), wherein said 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

R^3 is $-(CR^6R^7)_n(C_6$-C_{10} aryl) or $-(CR^6R^7)_n$(4-10 membered heterocyclic), wherein each of said C_6-C_{10} aryl and 4-10 membered heterocyclic moieties of said R^3 groups are optionally substituted with at least one R^5 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein said C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_6 alkyl, halo, $-OR^6$, $-CF_3$, and -CN;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl;

n is 0, 1, 2, 3, 4, or 5; and

t is 0, 1, 2, 3, 4, or 5; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, 3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, or 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethylpyridin-3-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one.

Still another aspect of the present invention provides compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is $-(CR^6R^7)_n$(5-6 membered heterocyclic), wherein said 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

R^3 is $-(CR^6R^7)_t(C_6-C_{10}$ aryl) or $-(CR^6R^7)_t$(4-10 membered heterocyclic), wherein said aryl and heterocyclic moieties of said R^3 groups are optionally substituted with at least one R^5 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein said C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_6 alkyl, halo, $-OR^6$, $-CF_3$, and -CN;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl;

n is 1 or 2; and

t is 1 or 2; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, 3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, or 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethylpyridin-3-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one.

Further provided are compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is $-(CR^6R^7)_t$(5-6 membered heterocyclic), wherein said 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

R^3 is $-(CR^6R^7)_t(C_6-C_{10}$ aryl) or $-(CR^6R^7)_t$(4-10 membered heterocyclic), wherein said aryl and heterocyclic moieties of said R^3 groups are optionally substituted with at least one R^5 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein said C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_6 alkyl, halo, $-OR^6$, $-CF_3$, and -CN;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl;

n is 2; and

t is 1 or 2; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, 3-[(6-

chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, or 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethylpyridin-3-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one.

In yet another aspect are afforded compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is $-(CR^6R^7)_t$(5-6 membered heterocyclic), wherein said 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

R^3 is $-(CR^6R^7)_t$(4-10 membered heterocyclic), optionally substituted with at least one R^5 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein said C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_6 alkyl, halo, $-OR^6$, $-CF_3$, and -CN;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl;

n is 2; and

t is 1 or 2; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, 3-[(8-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, or 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethylpyridin-3-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one.

Also provided herein are compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is $-(CR^6R^7)_t$(5-6 membered heterocyclic), wherein said 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

R^3 is $-(CR^6R^7)_t$(4-10 membered heterocyclic), optionally substituted with at least one R^5 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein said C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_6 alkyl, halo, $-OR^6$, $-CF_3$, and -CN;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl;

n is 2; and

t is 1; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, 3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, or 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethylpyridin-3-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one.

Yet another aspect provides compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is a $-(CH_2)_t$(pyridyl), $-(CH_2)_t$(pyrazolyl), $-(CH_2)_t$(pyrrolyl), $-(CH_2)_t$(oxazolyl), $-(CH_2)_t$(thiazolyl), $-(CH_2)_t$(imidazolyl), $-(CH_2)_t$(isoxazolyl), $-(CH_2)_t$(isothiazolyl), $-(CH_2)_t$(1,2,3-triazolyl), $-(CH_2)_t$(1,3,4-triazolyl), $-(CH_2)_t$(1,3,4-thiadiazolyl), $-(CH_2)_t$(pyridazinyl), $-(CH_2)_t$(pyrimidinyl), $-(CH_2)_t$(pyrazinyl), or $-(CH_2)_t$(1,3,5-triazinyl) group, each of which is optionally substituted with at least one R^4 group;

R^3 is $-(CR^6R^7)_t$(4-10 membered heterocyclic), optionally substituted with at least one R^5 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_8 alkyl, halo, $-OR^6$, $-CF_3$, and -CN;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl; and

t is 1 or 2; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, 3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, or 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethylpyridin-3-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one.

Further provided are compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is a $-(CH_2)_t$(pyridyl), $-(CH_2)_t$(pyrazolyl), $-(CH_2)_t$(pyrrolyl), $-(CH_2)_t$(oxazolyl), $-(CH_2)_t$(thiazolyl), $-(CH_2)_t$(imidazolyl), $-(CH_2)_t$(isoxazolyl), $-(CH_2)_t$(isothiazolyl), $-(CH_2)_t$(1,2,3-triazolyl), $-(CH_2)_t$(1,3,4-triazolyl), $-(CH_2)_t$(1,3,4-thiadiazolyl), -

$(CH_2)_{0-2}$(pyridazinyl), -$(CH_2)_{0-2}$(pyrimidinyl), –$(CH_2)_{0-2}$(pyrazinyl), or –$(CH_2)_{0-2}$(1,3,5-triazinyl) group, each of which is optionally substituted with at least one R^4 group;

R^3 is -$(CH_2)_{0-2}$(4-10 membered heterocyclic), optionally substituted with at least one R^5 group;

each R^4 is independently selected from halo, -OR^6, oxo, -NR^6R^7, -CF_3, -CN, -$C(O)R^6$, -$C(O)OR^6$, -$OC(O)R^6$, -$NR^6C(O)R^7$, -$NR^6C(O)OR^7$, -$NR^6C(O)NR^6R^7$, -$C(O)NR^6R^7$, -$SO_2NR^6R^7$, -$NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_8 alkyl, halo, -OR^6, -CF_3, and -CN; and

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, 3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, or 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethylpyridin-3-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one.

Still another aspect provides compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is a –$(CH_2)_{0-2}$(pyridyl), –$(CH_2)_{0-2}$(pyrazolyl), –$(CH_2)_{0-2}$(pyrrolyl), –$(CH_2)_{0-2}$(oxazolyl), -$(CH_2)_{0-2}$(thiazolyl), –$(CH_2)_{0-2}$(imidazolyl), –$(CH_2)_{0-2}$(isoxazolyl), –$(CH_2)_{0-2}$(isothiazolyl), -$(CH_2)_{0-2}$(1,2,3-triazolyl), –$(CH_2)_{0-2}$(1,3,4-triazolyl), –$(CH_2)_{0-2}$(1,3,4-thiadiazolyl), –$(CH_2)_{0-2}$(pyridazinyl), -$(CH_2)_{0-2}$(pyrimidinyl), –$(CH_2)_{0-2}$(pyrazinyl), or –$(CH_2)_{0-2}$(1,3,5-triazinyl) group, each of which is optionally substituted with at least one R^4 group;

R^3 is -$(CH_2)_{0-2}$([1,2,4]triazolo[1,5-a]pyrimidin-2-yl), optionally substituted with at least one R^5 group;

each R^4 is independently selected from halo, -OR^6, oxo, -NR^6R^7, -CF_3, -CN, -$C(O)R^6$, -$C(O)OR^6$, -$OC(O)R^6$, -$NR^6C(O)R^7$, -$NR^6C(O)OR^7$, -$NR^6C(O)NR^6R^7$, -$C(O)NR^6R^7$, -$SO_2NR^6R^7$, -$NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_8 alkyl, halo, -OR^6, -CF_3, and -CN; and

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, 3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-[2-(2-ethylpyridin-4-yl)ethyl]-

4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, or 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethylpyridin-3-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one.

Yet another aspect affords compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is a $-(CH_2)_{0-2}$(pyridyl), $-(CH_2)_{0-2}$(pyrazolyl), $-(CH_2)_{0-2}$(pyrrolyl), $-(CH_2)_{0-2}$(oxazolyl), $-(CH_2)_{0-2}$(thiazolyl), $-(CH_2)_{0-2}$(imidazolyl), $-(CH_2)_{0-2}$(isoxazolyl), $-(CH_2)_{0-2}$(isothiazolyl), $-(CH_2)_{0-2}$(1,2,3-triazolyl), $-(CH_2)_{0-2}$(1,3,4-triazolyl), $-(CH_2)_{0-2}$(1,3,4-thiadiazolyl), $-(CH_2)_{0-2}$(pyridazinyl), $-(CH_2)_{0-2}$(pyrimidinyl), $-(CH_2)_{0-2}$(pyrazinyl), or $-(CH_2)_{0-2}$(1,3,5-triazinyl0 group, each of which is optionally substituted with at least one R^4 group;

R^3 is $-(CH_2)$([1,2,4]triazolo[1,5-a]pyrimidin-2-yl), optionally substituted with at least one R^5 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_8 alkyl, halo, $-OR^6$, $-CF_3$, and -CN; and

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, 3-[(8-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, or 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethylpyridin-3-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one.

Further still are compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is $-(CH_2)_{0-2}$(pyridyl) or $-(CH_2)_{0-2}$(pyrazolyl), each of which is optionally substituted with at least one R^4 group;

R^3 is $-(CH_2)$([1,2,4]triazolo[1,5-a]pyrimidin-2-yl), optionally substituted with at least one R^5 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_8 alkyl, halo, $-OR^6$, $-CF_3$, and -CN; and

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, 3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, or 6-cyclopentyl-3-[[5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethylpyridin-3-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one.

In still another aspect are compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is $-(CH_2)_n$(pyridyl) or $-(CH_2)_n$(pyrazolyl), each of which is optionally substituted with at least one substituent selected from halo, C_1-C_6 alkyl, $-OR^6$, and $-NR^6R^7$;

R^3 is $-(CH_2)$([1,2,4]triazolo[1,5-a]pyrimidin-2-yl), optionally substituted with at least one substituent selected from halo and C_1-C_6 alkyl; and

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, 3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, or 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethylpyridin-3-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one.

Further still are provided compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is $-(CH_2)_n$(pyridyl) optionally substituted with at least one substituent selected from halo, C_1-C_6 alkyl, $-OR^6$, and $-NR^6R^7$;

R^3 is $-(CH_2)$([1,2,4]triazolo[1,5-a]pyrimidin-2-yl), optionally substituted with at least one substituent selected from halo and C_1-C_6 alkyl; and

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, 3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, or 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethylpyridin-3-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one.

Also provided are compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^6 is $-(CH_2)_n$(pyrazolyl) optionally substituted with at least one substituent selected from halo, C_1–C_6 alkyl, $-OR^6$, and $-NR^6R^7$;

R^5 is -(CH$_2$)([1,2,4]triazolo[1,5-a]pyrimidin-2-yl), optionally substituted with at least one substituent selected from halo and C_1–C_6 alkyl; and

each R^6 and R^7 is independently selected from hydrogen and C_1–C_6 alkyl; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, 3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, or 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethylpyridin-3-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one.

In yet another aspect are compounds selected from:

6-[2-(6-amino-5-ethyl-2-methylpyridin-3-yl)ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(4-ethylpyridin-2-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one;

6-cyclopentyl-6-[2-(4-ethylpyridin-2-yl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2*H*-pyran-2-one;

6-cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one;

6-cyclopentyl-6-[2-(2,6-dimethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-(2-isopropylpyridin-4-yl)ethyl]-5,6-dihydro-2*H*-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-6-isopropylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-6-methylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one;

6-cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2*H*-pyran-2-one;

6-cyclopentyl-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-propoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-6-[2-(2-ethyl-5-propoxypyridin-4-yl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;
6-{2-[2,6-bis(2,2,2-trifluoroethyl)pyridin-4-yl]ethyl}-6-cyclopentyl-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(6-ethyl-3-methoxypyridin-2-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(1-ethyl-1H-pyrazol-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-(1-isopropyl-1H-pyrazol-4-yl)ethyl]-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-(5-methoxy-2-methylpyridin-4-yl)ethyl]-5,6-dihydro-2H-pyran-2-one;
6-{2-[2,6-bis(2,2,2-trifluoroethyl)pyridin-4-yl]ethyl}-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
5-bromo-1-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)pyridin-2(1H)-one;
1-(2-[2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-5-ethylpyridin-2(1H)-one;
2-[3-chloro-5-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)pyridin-2-yl]-2-methylpropanenitrile;
(+)-6-{2-[2,6-bis(2,2,2-trifluoroethyl)pyridin-4-yl]ethyl}-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(-)-6-{2-[2,6-bis(2,2,2-trifluoroethyl)pyridin-4-yl]ethyl}-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(+)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(-)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

(+)-6-cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

(-)-6-cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

(+)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

(-)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

(+)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-propoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

(-)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-propoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

(+)-6-cyclopentyl-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one; and

(-)-6-cyclopentyl-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one; or pharmaceutically acceptable salts or solvates thereof.

A further aspect of the present invention provides compounds of formula (4),

wherein:

R^1 is cyclopentyl;

R^2 is $-(CR^6R^7)_n(C_6-C_{10}$ aryl) or $-(CR^6R^7)_n$(4-10 membered heterocyclic), wherein each of said C_6-C_{10} aryl and 4-10 membered heterocyclic groups is optionally substituted with at least one R^4 group;

R^3 is $-(CR^6R^7)_t$(4-10 membered heterocyclic) substituted with at least one R^5, and further optionally substituted with at least one C_1-C_6 alkyl;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein said C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl groups are optionally substituted with at least one R^6;

R^5 is halogen, oxo, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, and 4-10 membered heterocyclic substituted with R^6;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl;

n is 0, 1, 2, 3, 4, or 5; and

t is 0, 1, 2, 3, 4, or 5; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-[2-[4-(benzyloxy)phenyl]ethyl]-6-cyclopentyl-3-[[2-cyclopropyl-6-hydroxypyrimidin-4-yl]methyl]dihydro-2*H*-pyran-2,4(3*H*)-dione, methyl {5-[(6-cyclopentyl-6-[2-[4-(difluoromethyl)-3-fluorophenyl]ethyl]-2,4-dioxotetrahydro-2*H*-pyran-3-yl)methyl]isoxazol-3-yl}carbamate; or 6-[2-(5-chloro-2,4-dimethoxyphenyl)ethyl]-6-cyclopentyl-3-[[3-pyridin-2-yl-1,2,4-oxadiazol-5-yl)methyl]dihydro-2*H*-pyran-2,4(3*H*)-dione.

In yet another aspect are compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is $-(CR^6R^7)_n(C_6$-C_{10} aryl) or $-(CR^6R^7)_n$(4-10 membered heterocyclic), wherein each of said C_6-C_{10} aryl and 4-10 membered heterocyclic groups is optionally substituted with at least one R^4 group;

R^3 is $-(CH_2)_t$(4-10 membered heterocyclic) substituted with at least one R^5, and further optionally substituted with at least one C_1-C_6 alkyl;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein said C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl groups are optionally substituted with at least one R^5;

R^5 is halogen, oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, and 4-10 membered heterocyclic substituted with R^6;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl;

n is 0, 1, 2, 3, 4, or 5; and

t is 0, 1, 2, 3, 4, or 5; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-[2-[4-(benzyloxy)phenyl]ethyl]-6-cyclopentyl-3-[[2-cyclopropyl-6-hydroxypyrimidin-4-yl)methyl]dihydro-2*H*-pyran-2,4(3*H*)-dione, methyl {5-[(6-cyclopentyl-6-[2-[4-(difluoromethyl)-3-fluorophenyl]ethyl]-2,4-dioxotetrahydro-2*H*-pyran-3-yl)methyl]isoxazol-3-yl}carbamate; or 6-[2-(5-chloro-2,4-dimethoxyphenyl)ethyl]-6-cyclopentyl-3-[[3-pyridin-2-yl-1,2,4-oxadiazol-5-yl)methyl]dihydro-2*H*-pyran-2,4(3*H*)-dione.

Further provided are compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is $-(CH_2)_n(C_6$-C_{10} aryl) or $-(CH_2)_n$(4-10 membered heterocyclic), wherein each of said C_6-C_{10} aryl and 4-10 membered heterocyclic groups is optionally substituted with at least one R^4 group;

R^3 is $-(CH_2)_t$(4-10 membered heterocyclic) substituted with at least one R^5, and further optionally substituted with at least one C_1-C_6 alkyl;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

R^5 is halogen, oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, and 4-10 membered heterocyclo substituted with R^6;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl;

n is 0, 1, 2, 3, 4, or 5; and

t is 0, 1, 2, 3, 4, or 5; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-[2-[4-(benzyloxy)phenyl]ethyl]-6-cyclopentyl-3-[[2-cyclopropyl-6-hydroxypyrimidin-4-yl]methyl]dihydro-2*H*-pyran-2,4(3*H*)-dione, methyl [5-[[6-cyclopentyl-6-[2-[4-(difluoromethyl)-3-fluorophenyl]ethyl]-2,4-dioxotetrahydro-2*H*-pyran-3-yl]methyl]isoxazol-3-yl]carbamate; or 6-[2-(5-chloro-2,4-dimethoxyphenyl)ethyl]-6-cyclopentyl-3-[(3-pyridin-2-yl-1,2,4-oxadiazol-5-yl)methyl]dihydro-2*H*-pyran-2,4(3*H*)-dione.

In addition, herein are provided compounds selected from:

2-[4-(2-[2-cyclopentyl-5-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile;

ethyl 2-[(6-[2-[3-chloro-4-(1-cyano-1-methylethyl)phenyl]ethyl]-6-cyclopentyl-4-hydroxy-2-oxo-5,6-dihydro-2H-pyran-3-yl)methyl][1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate;

6-[2-(5-chloro-2,4-dimethoxyphenyl)ethyl]-6-cyclopentyl-4-hydroxy-3-[(1-methyl-3-pyrazin-2-yl-1H-1,2,4-triazol-5-yl)methyl]-5,6-dihydro-2H-pyran-2-one;

6-[2-(5-chloro-2,4-dimethoxyphenyl)ethyl]-6-cyclopentyl-4-hydroxy-3-[(1-methyl-3-pyridin-2-yl-1H-1,2,4-triazol-5-yl)methyl]-5,6-dihydro-2H-pyran-2-one;

6-[2-(5-chloro-2,4-dimethoxyphenyl)ethyl]-6-cyclopentyl-4-hydroxy-3-[(1-methyl-3-phenyl-1H-1,2,4-triazol-5-yl)methyl]-5,6-dihydro-2H-pyran-2-one;

2-[4-[2-(2-cyclopentyl-4-hydroxy-5-[[1-methyl-3-(6-methylpyridin-2-yl)-1H-1,2,4-triazol-5-yl]methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl]-2-fluorophenyl]-2-methylpropanenitrile;

2-[4-[2-(2-cyclopentyl-5-[[1,3-dimethyl-5-(4-methylpiperazin-1-yl)-1H-pyrazol-4-yl]methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl]-2-fluorophenyl]-2-methylpropanenitrile;

2-[4-(2-[2-cyclopentyl-4-hydroxy-5-[(1-methyl-3-pyrazin-2-yl-1H-1,2,4-triazol-5-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile;

2-[4-(2-[2-cyclopentyl-5-[(3-ethyl-1-methyl-5-morpholin-4-yl-1H-pyrazol-4-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile;

2-{4-(2-[2-cyclopentyl-5-[(1,3-dimethyl-5-morpholin-4-yl-1H-pyrazol-4-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile; and
2-{4-[2-(2-cyclopentyl-5-[[3-(difluoromethyl)-5-(dimethylamino)-1-methyl-1H-pyrazol-4-yl]methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl]-2-fluorophenyl}-2-methylpropanenitrile; or
pharmaceutically acceptable salts or solvates thereof.

In a still further aspect of the present invention are afforded compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is $-(CR^6R^7)_n(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is substituted with at least one R^{4a} group, and is optionally substituted with at least one R^{4b} group;

R^3 is $-(CR^6R^7)_t(C_6$-C_{10} aryl) or $-(CR^6R^7)_t$(4-10 membered heterocyclic), wherein said aryl and heterocyclic moieties of said R^3 groups are optionally substituted with at least one R^5 group;

each R^{4a} is independently selected from –O(4-10 membered heterocyclic), -S(4-10 membered heterocyclic), and $-(CR^6R^7)_t$(4-10 membered heterocyclic);

each R^{4b} is independently selected from halo, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein said C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_6 alkyl, halo, $-OR^6$, $-CF_3$, and -CN;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl;

n is 0, 1, 2, 3, 4, or 5; and

t is 0, 1, 2, 3, 4, or 5; or

pharmaceutically acceptable salts or solvates thereof.

Another aspect provides compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is $-(CH_2)_n(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is substituted with at least one R^{4a} group, and is optionally substituted with at least one R^{4b} group;

R^3 is $-(CR^6R^7)_t(C_6$-C_{10} aryl) or $-(CR^6R^7)_t$(4-10 membered heterocyclic), wherein said aryl and heterocyclic moieties of said R^3 groups are optionally substituted with at least one R^5 group;

each R^{4a} is independently selected from –O(4-10 membered heterocyclic), -S(4-10 membered heterocyclic), and $-(CR^6R^7)_t$(4-10 membered heterocyclic);

each R^{4b} is independently selected from halo, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein said C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_6 alkyl, halo, $-OR^6$, $-CF_3$, and -CN;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl; and

t is 0, 1, 2, 3, 4, or 5; or

pharmaceutically acceptable salts or solvates thereof.

Also provided herein are compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is $-(CH_2)_t(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is substituted with at least one R^{4a} group, and is optionally substituted with at least one R^{4b} group;

R^3 is $-(CH_2)_t(C_6$-C_{10} aryl) or $-(CH_2)_t$(4-10 membered heterocyclic), wherein said aryl and heterocyclic moieties of said R^3 groups are optionally substituted with at least one R^5 group;

each R^{4a} is independently selected from –O(4-10 membered heterocyclic), -S(4-10 membered heterocyclic), and $-(CR^6R^7)_t$(4-10 membered heterocyclic);

each R^{4b} is independently selected from halo, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein said C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_6 alkyl, halo, $-OR^6$, $-CF_3$, and -CN;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl; and

t is 0 or 1; or

pharmaceutically acceptable salts or solvates thereof.

Further still, provided herein are compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is $-(CH_2)_t(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is substituted with at least one R^{4a} group, and is optionally substituted with at least one R^{4b} group;

R^3 is $-(CH_2)_t$(4-10 membered heterocyclic), wherein said aryl and heterocyclic moieties of said R^3 groups are optionally substituted with at least one R^5 group;

each R^{4a} is independently selected from –O(4-10 membered heterocyclic), -S(4-10 membered heterocyclic), and $-(CR^6R^7)_t$(4-10 membered heterocyclic);

each R^{4b} is independently selected from halo, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$,

$-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_8 alkyl, halo, $-OR^6$, $-CF_3$, and -CN;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl; and

t is 0 or 1; or

pharmaceutically acceptable salts or solvates thereof.

In yet another aspect are compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is $-(CH_2)_t(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is substituted with at least one R^{4a} group, and is optionally substituted with at least one R^{4b} group;

R^3 is -(CH$_2$)([1,2,4]triazolo[1,5-a]pyrimidin-2-yl), optionally substituted with at least one substituent selected from halo and C_1-C_8 alkyl;

each R^{4a} is independently selected from –O(4-10 membered heterocyclic), -S(4-10 membered heterocyclic), and $-(CR^6R^7)_t$(4-10 membered heterocyclic);

each R^{4b} is independently selected from halo, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_8 alkyl, halo, $-OR^6$, $-CF_3$, and -CN;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl; and

t is 0 or 1; or

pharmaceutically acceptable salts or solvates thereof.

Further still are compounds of formula (4), wherein:

R^1 is cyclopentyl;

R^2 is $-(CH_2)_t(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is substituted with at least one R^{4a} group, and is optionally substituted with at least one R^{4b} group;

R^3 is -(CH$_2$)([1,2,4]triazolo[1,5-a]pyrimidin-2-yl), substituted with at least one substituent selected from halo and C_1-C_8 alkyl;

each R^{4a} is independently selected from –O(4-10 membered heterocyclic), -S(4-10 membered heterocyclic), and $-(CR^6R^7)_t$(4-10 membered heterocyclic);

each R^{4b} is independently selected from halo, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_8 alkyl, halo, $-OR^6$, $-CF_3$, and -CN;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl; and

t is 0 or 1; or

pharmaceutically acceptable salts or solvates thereof.

Also provided are compounds selected from:

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(1H-1,2,4-triazol-1-ylmethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(1H-pyrazol-1-ylmethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-6-[2-[3-ethyl-4-(1H-pyrazol-1-ylmethyl)phenyl]ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(1,3-thiazol-2-yloxy)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(morpholin-4-ylmethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-6-[2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl]-4-hydroxy-3-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-6-[2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;

(+)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

(-)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one; and

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(pyrrolidin-1-ylmethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one; or

pharmaceutically acceptable salts or solvates thereof.

In yet a further aspect of the present invention are provided compounds selected from:

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethyl-4-hydroxy-2-propoxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenyl]acetonitrile;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(3-ethyl-4-methylphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

(6R)-6-cyclopentyl-6-[2-(5-ethyl-2,4-dihydroxyphenyl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethoxy-5-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-methoxy-3-(trifluoromethyl)phenyl]ethyl]-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethyl-2,4-dimethoxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-6-[2-(2-ethoxy-5-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethyl-4-hydroxy-2-isopropoxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxyphenyl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethyl-2-hydroxy-4-propoxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-6-[2-(5-ethyl-2-hydroxy-4-propoxyphenyl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethyl-4-hydroxy-2-isobutoxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-hydroxy-3-methyl-5-(2,2,2-trifluoroethyl)phenyl]ethyl]-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-hydroxy-2-propoxy-5-(2,2,2-trifluoroethyl)phenyl]ethyl]-5,6-dihydro-2H-pyran-2-one;
2-[4-(2-[2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-methylphenyl]-2-methylpropanenitrile;
2-[4-(2-[2-cyclopentyl-5-[(1,3-dimethyl-1H-1,2,4-triazol-5-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile;
2-[4-(2-[2-cyclopentyl-5-[(1,3-dimethyl-1H-pyrazol-4-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile;
2-[4-(2-[2-cyclopentyl-4-hydroxy-5-[(1-methyl-1H-pyrazol-4-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile;
2-[4-(2-[2-cyclopentyl-4-hydroxy-6-oxo-5-[(1,3,5-trimethyl-1H-pyrazol-4-yl)methyl]-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile;

2-[4-(2-[2-cyclopentyl-5-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile;

2-[4-(2-[2-cyclopentyl-5-[(1-ethyl-3-methyl-1H-pyrazol-4-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile;

2-[4-(2-[5-[(5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile;

2-[4-[2-(5-[[5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl]-2-fluorophenyl]-2-methylpropanenitrile;

2-(2-chloro-4-[2-[2-cyclopentyl-4-hydroxy-5-(imidazo[1,2-b][1,2,4]triazin-6-ylmethyl)-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]phenyl)-2-methylpropanenitrile;

6-[2-(5-chloro-2,4-dimethoxyphenyl)ethyl]-6-cyclopentyl-3-[(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

6-[2-(3-chloro-4-isopropoxyphenyl)ethyl]-6-cyclopentyl-3-[(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

2-[4-(2-[2-cyclopentyl-5-[(2-ethyl-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile;

2-[2-chloro-4-(2-[2-cyclopentyl-5-[(1,3-dimethyl-1H-1,2,4-triazol-5-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)phenyl]-2-methylpropanenitrile;

2-[2-chloro-4-(2-[2-cyclopentyl-5-[(1-ethyl-1H-pyrazol-4-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)phenyl]-2-methylpropanenitrile;

2-[2-chloro-4-(2-[2-cyclopentyl-4-hydroxy-5-[(1-methyl-1H-pyrazol-4-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)phenyl]-2-methylpropanenitrile;

2-[2-chloro-4-(2-[2-cyclopentyl-4-hydroxy-6-oxo-5-[(1,3,5-trimethyl-1H-pyrazol-4-yl)methyl]-3,6-dihydro-2H-pyran-2-yl]ethyl)phenyl]-2-methylpropanenitrile;

2-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-(trifluoromethyl)phenyl]-2-methylpropanenitrile;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-hydroxy-3-(trifluoromethyl)phenyl]ethyl]-5,6-dihydro-2H-pyran-2-one;

2-[4-(2-[2-cyclopentyl-4-hydroxy-6-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluoro-5-hydroxyphenyl]-2-methylpropanenitrile;

[4-(2-[2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenyl]acetonitrile;

[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-(trifluoromethyl)phenyl]acetonitrile;

2-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-(trifluoromethyl)phenyl]-2-ethylbutanenitrile;
2-[4-(2-[2-cyclopentyl-5-[(3-ethyl-1-methyl-1H-1,2,4-triazol-5-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile;
2-[4-(2-[2-cyclopentyl-5-[(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile; and
2-[4-(2-[2-cyclopentyl-5-[(1-ethyl-5-methyl-1H-1,2,4-triazol-3-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile; or
pharmaceutically acceptable salts or solvates thereof.

In yet another aspect of the present invention are afforded compounds selected from:
(+)-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenyl]acetonitrile;
(-)-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenyl]acetonitrile;
(+)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethyl-4-hydroxy-2,3-dihydro-1-benzofuran-7-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(-)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethyl-4-hydroxy-2,3-dihydro-1-benzofuran-7-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(+)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethoxy-5-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(-)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethoxy-5-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(+)-6-cyclopentyl-6-[2-(2-ethoxy-5-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;
(-)-6-cyclopentyl-6-[2-(2-ethoxy-5-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;
(+)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-hydroxy-3-(2,2,2-trifluoroethyl)phenyl]ethyl]-5,6-dihydro-2H-pyran-2-one; and
(-)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-hydroxy-3-(2,2,2-trifluoroethyl)phenyl]ethyl]-5,6-dihydro-2H-pyran-2-one; or
pharmaceutically acceptable salts or solvates thereof.

Furthermore, the present invention comprises compounds selected from:
N-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenyl]methanesulfonamide;

N-[4-(2-[2-cyclopentyl-4-hydroxy-6-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenyl]methanesulfonamide;

N-(4-[2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl]-2-ethylphenyl)methanesulfonamide;

N-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenyl]ethanesulfonamide;

N-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenyl]propane-1-sulfonamide;

methyl 4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylbenzoate;

6-cyclopentyl-6-[2-(4-[(dimethylamino)methyl]-3-ethylphenyl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(methoxymethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethyl-N-methylbenzamide;

6-[2-[4-(aminomethyl)-3-ethylphenyl]ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

tert-butyl 4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylbenzylcarbamate;

6-cyclopentyl-6-[2-(4-[[(cyclopropylmethyl)amino]methyl]-3-ethylphenyl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

N-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylbenzyl]methanesulfonamide;

N-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylbenzyl]acetamide;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[5-ethyl-2-(3-methoxypropyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(3-methoxypropyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

N-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorobenzyl]acetamide;

N-[1-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-1-methylethyl]methanesulfonamide;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[4-(ethylsulfonyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-[(trifluoromethyl)sulfonyl]phenyl]ethyl)-5,6-dihydro-2H-pyran-2-one;
tert-butyl 2-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenoxy]ethyl(methyl)carbamate;
tert-butyl 2-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenoxy]ethylcarbamate;
6-[2-[4-(2-aminoethoxy)-3-ethylphenyl]ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-(2-[3-ethyl-4-[2-(methylamino)ethoxy]phenyl]ethyl)-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[5-fluoro-4-(hydroxymethyl)-2-methoxyphenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
N-[(1R)-1-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)phenyl]ethyl]ethanesulfonamide;
N-[(1R)-1-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)phenyl]ethyl]-2,2,2-trifluoroethanesulfonamide;
N-[(1R)-1-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)phenyl]ethyl]methanesulfonamide;
tert-butyl (1R)-1-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)phenyl]ethylcarbamate;
6-(2-[4-[(1R)-1-aminoethyl]phenyl]ethyl)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-[2-(5-acetyl-4-hydroxy-2-methoxyphenyl)ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-[2-[3-chloro-4-(methylsulfonyl)phenyl]ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorobenzoic acid;
2-chloro-4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)benzoic acid;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-(1-hydroxy-1-methylethyl)-3-methylphenyl]ethyl]-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(hydroxymethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-[2-[3-chloro-4-(1-hydroxy-1-methylethyl)phenyl]ethyl]-6-cyclopentyl-4-hydroxy-3-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-5,6-dihydro-2H-pyran-2-one;
6-[2-[3-chloro-4-(1-hydroxy-1-methylethyl)phenyl]ethyl]-6-cyclopentyl-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;
6-[2-[3-chloro-4-(1-hydroxy-1-methylethyl)phenyl]ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-[2-[3-chloro-4-(1-hydroxy-1-methylethyl)phenyl]ethyl]-3-[(8-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-(methylsulfonyl)-3-(trifluoromethyl)phenyl]ethyl]-5,6-dihydro-2H-pyran-2-one;
methyl 4-[2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-2-fluorobenzoate; and
methyl 2-chloro-4-[2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]benzoate; or
pharmaceutically acceptable salts or solvates thereof.

In still another aspect are compounds selected from:
(+)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(hydroxymethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(-)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(hydroxymethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(+)-N-[4-[2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-2-ethylbenzyl]methanesulfonamide;
(-)-N-[4-[2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-2-ethylbenzyl]methanesulfonamide;
(+)-N-[4-[2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-2-ethylbenzyl]acetamide;
(-)-N-[4-[2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-2-ethylbenzyl]acetamide;
(+)-6-cyclopentyl-6-[2-[4-[(dimethylamino)methyl]-3-ethylphenyl]ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one; and
(-)-6-cyclopentyl-6-[2-[4-[(dimethylamino)methyl]-3-ethylphenyl]ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one; or
pharmaceutically acceptable salts or solvates thereof.

Further afforded are compounds selected from:

{4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-ethylphenyl}acetonitrile;

N-[4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-ethylphenyl]methanesulfonamide;

6-cyclopentyl-6-[2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl]dihydro-2H-pyran-2,4(3H)-dione;

N-((1R)-1-{4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]phenyl}ethyl)ethanesulfonamide;

6-cyclopentyl-6-[2-[3-fluoro-4-(methylsulfonyl)phenyl]ethyl]dihydro-2H-pyran-2,4(3H)-dione;

6-cyclopentyl-6-[2-[4-[(trifluoromethyl)sulfonyl]phenyl]ethyl]dihydro-2H-pyran-2,4(3H)-dione;

tert-butyl 2-{4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-ethylphenoxy}ethyl(methyl)carbamate;

tert-butyl 2-{4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-ethylphenoxy}ethylcarbamate;

tert-butyl 2-{4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-ethyl-5-methoxyphenoxy}ethyl(methyl)carbamate;

N-((1R)-1-{4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]phenyl}ethyl)-2,2,2-trifluoroethanesulfonamide;

tert-butyl (1R)-1-{4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]phenyl}ethylcarbamate;

6-[2-(5-acetyl-4-hydroxy-2-methoxyphenyl)ethyl]-6-cyclopentyldihydro-2H-pyran-2,4(3H)-dione;

2-chloro-4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]benzoic acid;

6-[2-[3-chloro-4-(methylsulfonyl)phenyl]ethyl]-6-cyclopentyldihydro-2H-pyran-2,4(3H)-dione;

6-cyclopentyl-6-[2-[4-(methylsulfonyl)-3-(trifluoromethyl)phenyl]ethyl]dihydro-2H-pyran-2,4(3H)-dione;

6-cyclopentyl-6-[2-[3-ethyl-4-(hydroxymethyl)phenyl]ethyl]dihydro-2H-pyran-2,4(3H)-dione;

methyl 4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-fluorobenzoate;

4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-fluorobenzoic acid;

methyl 2-chloro-4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]benzoate;

2-[4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)phenyl]-2-methylpropanenitrile;

[4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)phenyl]acetonitrile;

1-[4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)phenyl]cyclopropanecarbonitrile;

2-[4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)phenyl]-2-ethylbutanenitrile;
tert-butyl 4-[4-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)butyl]piperidine-1-carboxylate;
6-cyclopentyl-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]dihydro-2H-pyran-2,4(3H)-dione;
6-cyclopentyl-6-[2-(6-ethyl-3-methoxypyridin-2-yl)ethyl]dihydro-2H-pyran-2,4(3H)-dione;
6-cyclopentyl-6-[2-(5-methoxy-2-methylpyridin-4-yl)ethyl]dihydro-2H-pyran-2,4(3H)-dione; and
2-[3-chloro-5-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]pyridin-2-yl]-2-methylpropanenitrile; or
pharmaceutically acceptable salts or solvates thereof.

The present invention also affords compounds selected from:
6-cyclopentyl-6-[2-[2-(cyclopropylmethoxy)-5-ethyl-4-hydroxyphenyl]ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-[2-[2-(cyclobutylmethoxy)-5-ethyl-4-hydroxyphenyl]ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
1-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)phenyl]cyclopropanecarbonitrile;
3-[(2-amino-7H-purin-6-yl)thio]-6-[2-(5-chloro-2,4-dimethoxyphenyl)ethyl]-6-cyclopentyldihydro-2H-pyran-2,4(3H)-dione;
2-[2-chloro-4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)(methyl)amino]-4,6-dioxotetrahydro-2H-pyran-2-yl]ethyl)phenyl]-2-methylpropanenitrile;
2-[2-chloro-4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)oxy]-4,6-dioxotetrahydro-2H-pyran-2-yl]ethyl)phenyl]-2-methylpropanenitrile;
1-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-(trifluoromethyl)phenyl]cyclopropanecarbonitrile;
tert-butyl 4-(4-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]butyl)piperidine-1-carboxylate; and
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-(4-piperidin-4-ylbutyl)-5,6-dihydro-2H-pyran-2-one; or
pharmaceutically acceptable salts or solvates thereof.

The invention also relates to a method for the treatment of Hepatitis C virus (HCV) in a mammal, such as a human, comprising administering to said mammal an amount of a compound of the present invention or a salt or solvate thereof that is effective in treating HCV.

In a further aspect of the present invention are provided methods for the treatment of a mammal, such as a human, suffering from infection with Hepatitis C virus, comprising administering to said mammal a Hepatitis C virus-inhibiting amount of a compound of the

present invention, or a pharmaceutically acceptable salt, prodrug, pharmaceutically active metabolite, or solvate thereof.

The present invention also relates to a method of inhibiting Hepatitis C polymerase, comprising contacting said polymerase with a polymerase-inhibiting amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, pharmaceutically active metabolite, or solvate thereof.

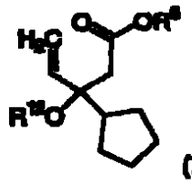
The present invention is also directed to a pharmaceutical composition for the treatment of Hepatitis C virus (HCV) in a mammal, such as a human, comprising an amount of a compound the present invention, or a pharmaceutically acceptable salt, prodrug, pharmaceutically active metabolite, or solvate thereof, that is effective in treating Hepatitis C virus in an infected mammal, and a pharmaceutically acceptable carrier.

The present invention is also directed to inhibition of Hepatitis C virus replication in a mammal, such as a human, comprising administering to said mammal a Hepatitis C virus replication-inhibiting amount of a compound of the present invention.

The present invention is further directed to a method of inhibiting Hepatitis C virus RdRp protein activity, comprising contacting the protein with an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, pharmaceutically active metabolite, or solvate thereof. For Example, HCV activity may be inhibited in mammalian tissue by administering an HCV-inhibiting agent according to the invention.

The present invention also relates to the use of the compounds of the invention in the preparation of a medicament for the treatment of a mammal suffering from infection with Hepatitis C virus. The medicament may comprise a Hepatitis C virus-inhibiting amount of a compound or compounds of the invention and a pharmaceutically acceptable carrier or carriers.

In a further aspect of the present invention are provided compounds of formula (7),



(7)

wherein:

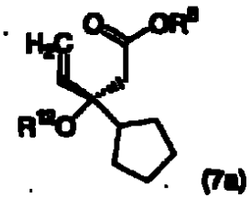
R^9 is hydrogen or C_1–C_6 alkyl;

R^{12} is hydrogen or –C(O)R^{13}; and

R^{13} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$;

or a salt thereof.

Also provided herein are compounds of formula (7a),



(7a)

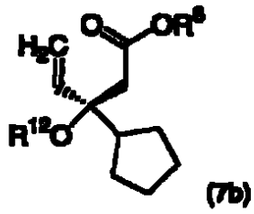
R^9 is hydrogen or C_1-C_8 alkyl;

R^{12} is hydrogen or $-C(O)R^{13}$; and

R^{13} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$;

or a salt thereof.

In yet another aspect are compounds of formula (7b),



(7b)

R^9 is hydrogen or C_1-C_8 alkyl;

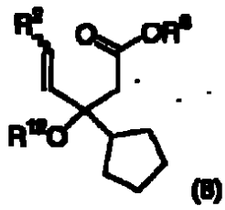
R^{12} is hydrogen or $-C(O)R^{13}$; and

R^{13} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$;

or a salt thereof.

Still further are provided any of the above compounds of formula (7), (7a), or (7b), wherein R^9 is hydrogen or any of the compounds wherein R^9 is C_1-C_8 alkyl.

Further provided herein are compounds of formula (8),



(6)

wherein:

R^2 is $-(CR^6R^7)_n$$C_6$-$C_{10}$ aryl or $-(CR^6R^7)_n$(5-6 membered heterocyclic), wherein said C_6-C_{10} aryl or 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

R^5 is oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN, and 4-10 membered heterocyclic substituted with R^6;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl;

R^9 is hydrogen or C_1-C_8 alkyl;

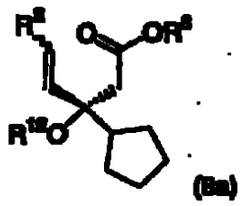
R^{10} is hydrogen or $-C(O)R^{15}$;

R^{15} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$; and

n is 0, 1, 2, 3, 4, or 5;

or a salt thereof.

In still another aspect are provided compounds of formula (6a),



(6a)

wherein:

R^2 is $-(CR^6R^7)_n$$C_6$-$C_{10}$ aryl or $-(CR^6R^7)_n$(5-6 membered heterocyclic), wherein said C_6-C_{10} aryl or 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$,

$-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^8;

R^8 is oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN, and 4-10 membered heterocyclic substituted with R^9;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl;

R^9 is hydrogen or C_1-C_8 alkyl; and

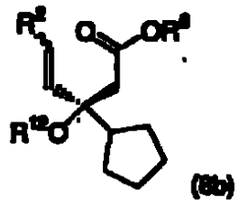
R^{10} is hydrogen or $-C(O)R^{12}$;

R^{12} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$; and

n is 0, 1, 2, 3, 4, or 5;

or a salt thereof.

Further provided herein are compounds of formula (8b),



(8b)

wherein:

R^2 is $-(CR^6R^7)_n$$C_6$-$C_{10}$ aryl or $-(CR^6R^7)_n$(5-6 membered heterocyclic), wherein said C_6-C_{10} aryl or 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^8;

R^8 is oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN, and 4-10 membered heterocyclic substituted with R^9;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl;

R^9 is hydrogen or C_1-C_8 alkyl; and

R^{10} is hydrogen or $-C(O)R^{12}$;

R^{12} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$; and

n is 0, 1, 2, 3, 4, or 5;

or a salt thereof.

Still further included herein are any of the above of formula (8), (8a), or (8b), wherein:

R^2 is $-(CR^6R^7)_nC_6$-C_{10} aryl, optionally substituted with at least one R^4 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

R^5 is oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN, and 4-10 membered heterocyclic substituted with R^6;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl;

R^9 is hydrogen or C_1-C_8 alkyl; and

R^{12} is hydrogen or $-C(O)R^{13}$;

R^{13} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$; and

n is 0, 1, 2, 3, 4, or 5;

or a salt thereof.

Still further included herein are any of the above of formula (8), (8a), or (8b), wherein:

R^2 is C_6-C_{10} aryl substituted with at least one substituent selected from halo, $-OR^6$, $-CF_3$, -CN, and C_1-C_8 alkyl, wherein said C_1-C_8 alkyl is optionally substituted with at least one R^5;

R^5 is oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN, and 4-10 membered heterocyclic substituted with R^6;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl; and

R^9 is hydrogen or C_1-C_8 alkyl;

R^{12} is hydrogen or $-C(O)R^{13}$; and

R^{13} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$;

or a salt thereof.

Still further included herein are any of the above of formula (8), (8a), or (8b), wherein:

R^2 is C_6-C_{10} aryl substituted with halo and $-C(CH_3)_2CN$; and

R^9 is hydrogen or C_1-C_8 alkyl; and

R^{12} is hydrogen;

or a salt thereof.

Still further included herein are any of the above of formula (8), (8a), or (8b), wherein, wherein:

R^8 is C_6-C_{10} aryl substituted with fluorine and $-C(CH_3)_2CN$; and

R^9 is hydrogen or C_1-C_6 alkyl; and

R^{12} is hydrogen;

or a salt thereof.

Still further included herein are any of the above of formula (8), (8a), or (8b), wherein:

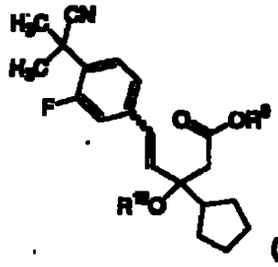
R^8 is C_6-C_{10} aryl substituted with chlorine and $-C(CH_3)_2CN$; and

R^9 is hydrogen or C_1-C_6 alkyl; and

R^{12} is hydrogen;

or a salt thereof.

The present invention also affords compounds of formula (8c),



(8c)

wherein;

R^9 is hydrogen or C_1-C_6 alkyl;

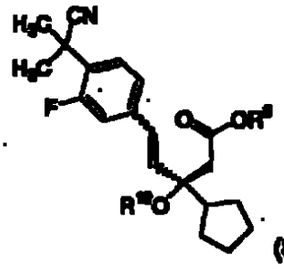
R^{12} is hydrogen or $-C(O)R^{13}$; and

R^{13} is C_1-C_6 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_6 alkyl$)_2$;

or a salt thereof.

Further provided herein are compounds of formula (8c), wherein R^{12} is hydrogen; or a salt thereof.

In another aspect of the present invention are provides compounds of formula (8d),



(8d)

wherein:

R^9 is hydrogen or C_1-C_6 alkyl;

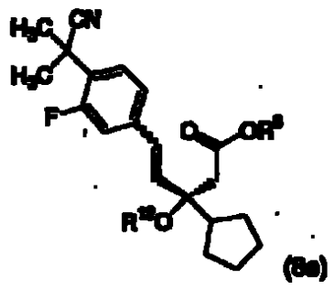
R^{12} is hydrogen or $-C(O)R^{13}$; and

R^{13} is C_1-C_6 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, $-OH$, $-OCH_3$, and $-N(C_1$-C_6 alkyl$)_2$;

or a salt thereof.

Also provided herein are compounds of formula (8d), wherein R^{12} is hydrogen; or a salt thereof.

The present invention further provides compounds of formula (8e),



(8e)

wherein:

R^9 is hydrogen or C_1-C_6 alkyl;

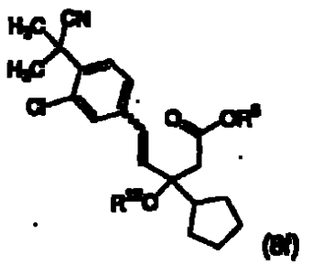
R^{12} is hydrogen or $-C(O)R^{13}$; and

R^{13} is C_1-C_6 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, $-OH$, $-OCH_3$, and $-N(C_1$-C_6 alkyl$)_2$;

or a salt thereof.

In an additional aspect are compounds of formula (8e), or a salt thereof, wherein R^{12} is hydrogen.

In still an additional aspect of the present invention are afforded compounds of formula (8f),



(8f)

wherein:

R^9 is hydrogen or C_1-C_6 alkyl;

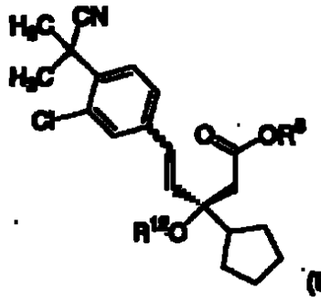
R^{12} is hydrogen or $-C(O)R^{13}$; and

R^{13} is C_1-C_6 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_6 alkyl$)_2$;

or a salt thereof.

Additionally provided are compounds of formula (8f), or a salt thereof, wherein R^{12} is hydrogen.

In yet another aspect are provided compounds of formula (8g),



(8g)

wherein:

R^9 is hydrogen or C_1-C_6 alkyl;

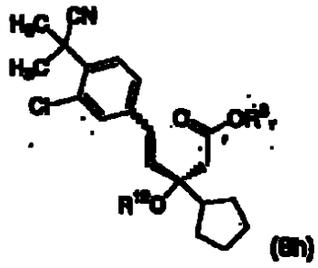
R^{12} is hydrogen or $-C(O)R^{13}$; and

R^{13} is C_1-C_6 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_6 alkyl$)_2$;

or a salt thereof.

Further still are compounds of formula (8g), or a salt thereof, wherein R^{12} is hydrogen.

In a further aspect of the present invention are provided compounds of formula (8h),



(8h)

wherein:

R^9 is hydrogen or C_1-C_6 alkyl;

R^{12} is hydrogen or $-C(O)R^{13}$; and

R^{13} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, $-OH$, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$;

or a salt thereof.

In still another aspect are compounds of formula (6h), or a salt thereof, wherein R^{12} is hydrogen.

The present invention also affords compounds according to any one of formula (6), (6a), (6b), (6c), (6d), (6e), (6f), (6g), and (6h), wherein R^9 is hydrogen, or any of those compounds wherein R^9 is C_1-C_8 alkyl.

Further provided herein are compounds of formula (6), (6a), or (6b), wherein:

R^2 is $-(CR^6R^7)_n$(5-6 membered heterocyclic), optionally substituted with at least one R^4 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, $-CN$, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

R^5 is oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, $-CN$, and 4-10 membered heterocyclic substituted with R^6;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl;

R^9 is hydrogen or C_1-C_8 alkyl; and

n is 0, 1, 2, 3, 4, or 5.

Further provided herein are compounds of formula (6), (6a), or (6b), wherein:

R^2 is -(5-6 membered heterocyclic), optionally substituted with at least one R^4 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, $-CN$, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

R^5 is oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, $-CN$, and 4-10 membered heterocyclic substituted with R^6;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl; and

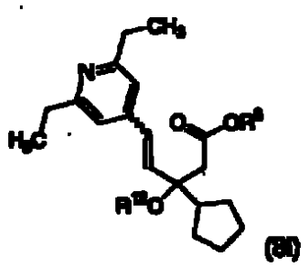
R^9 is hydrogen or C_1-C_8 alkyl.

Further provided herein are compounds of formula (6), (6a), or (6b), wherein:

R^2 is –(4-pyridyl), substituted with at least one C_1-C_8 alkyl; and

R^9 is hydrogen or C_1-C_8 alkyl.

Also provided herein are compounds of formula (6i),



(6l)

wherein:

R^8 is hydrogen or C_1-C_8 alkyl;

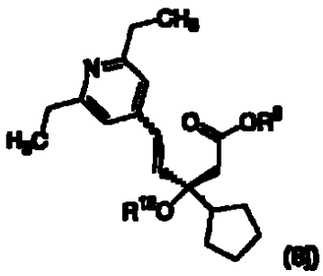
R^{12} is hydrogen or $-C(O)R^{13}$; and

R^{13} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$;

or a salt thereof.

Further provided herein are compounds of formula (6l), or a salt thereof, wherein R^{12} is hydrogen.

In still a further aspect of the present invention are afforded compounds of formula (6l).



(6l)

wherein:

R^8 is hydrogen or C_1-C_8 alkyl;

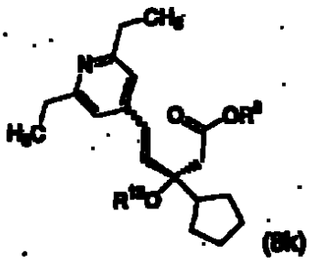
R^{12} is hydrogen or $-C(O)R^{13}$; and

R^{13} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$;

or a salt thereof.

Further afforded herein are compounds of formula (6l), or a salt thereof, wherein R^{12} is hydrogen.

Another aspect of the present invention provides compounds of formula (6k),



(6k)

wherein:

R^9 is hydrogen or C_1-C_6 alkyl;

R^{12} is hydrogen or $-C(O)R^{13}$; and

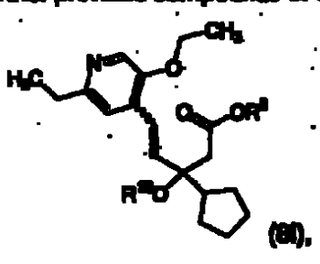
R^{13} is C_1-C_6 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_6 alkyl$)_2$;

or a salt thereof.

Further provided herein are compounds of formula (6k), or a salt thereof, wherein R^{12} is hydrogen.

Also provided herein are compounds according to any one of formula (6i), (6j), or (6k), wherein R^9 is hydrogen, or wherein R^9 is C_1-C_6 alkyl.

The present invention further provides compounds of formula (6l),



(6l),

wherein:

R^9 is hydrogen or C_1-C_6 alkyl;

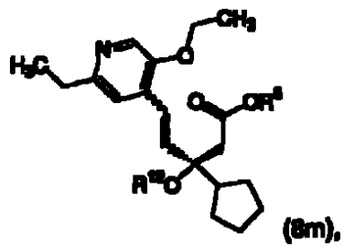
R^{12} is hydrogen or $-C(O)R^{13}$; and

R^{13} is C_1-C_6 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_6 alkyl$)_2$;

or a salt thereof.

Also afforded herein are compounds of formula (6l), or a salt thereof, wherein R^{12} is hydrogen.

In yet a further aspect of the present invention are provided compounds of formula (6m),



(8m),

wherein:

R^9 is hydrogen or C_1-C_8 alkyl;

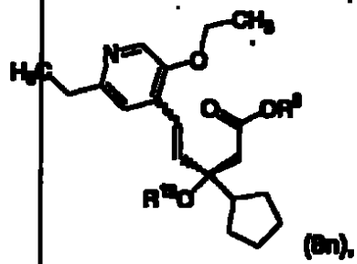
R^{12} is hydrogen or $-C(O)R^{13}$; and

R^{13} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH; $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$;

or a salt thereof.

Further provided herein are compounds of formula (8m), or a salt thereof, wherein R^{12} is hydrogen.

The present invention further affords compounds of formula (8n),



(8n),

wherein:

R^9 is hydrogen or C_1-C_8 alkyl;

R^{12} is hydrogen or $-C(O)R^{13}$; and

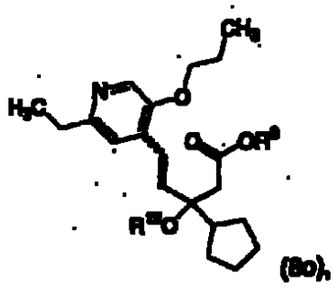
R^{13} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$;

or a salt thereof.

Also afforded herein are compounds of formula (8n), or a salt thereof, wherein R^{12} is hydrogen.

Further provided herein are compounds according to any one of formula (8l), (8m), or i), wherein R^9 is hydrogen, or wherein R^9 is C_1-C_8 alkyl.

The present invention also provides compounds of formula (8o),



(8o),

wherein:

R^9 is hydrogen or C_1-C_6 alkyl;

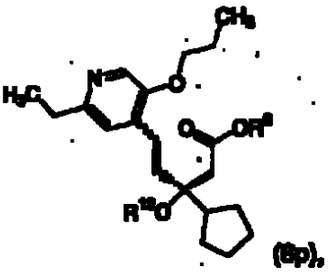
R^{10} is hydrogen or $-C(O)R^{15}$; and

R^{15} is C_1-C_6 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen; C_1-C_6 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_6 alkyl$)_2$;

or a salt thereof.

Further provided herein are compounds of formula (8o), or a salt thereof, wherein R^{10} is hydrogen.

Also provided herein are compounds of formula (8p),



(8p),

wherein:

R^9 is hydrogen or C_1-C_6 alkyl;

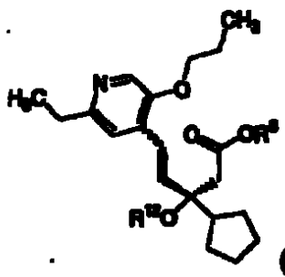
R^{10} is hydrogen or $-C(O)R^{15}$; and

R^{15} is C_1-C_6 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_6 alkyl$)_2$;

or a salt thereof.

Also afforded herein are compounds of formula (8p), or a salt thereof, wherein R^{10} is hydrogen.

Further provided herein are compounds of formula (8q),



(Bq),

wherein:

R^6 is hydrogen or C_1-C_8 alkyl;

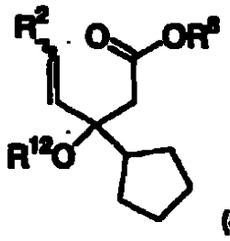
R^{12} is hydrogen or $-C(O)R^{13}$; and

R^{13} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$;

or a salt thereof.

Also afforded herein are compounds of formula (Bq), or a salt thereof, wherein R^{12} is hydrogen.

The present invention further provides methods of preparing compounds of formula (B),



(B)

wherein:

R^2 is $-(CR^6R^7)_n$$C_6$-$C_{10}$ aryl or $-(CR^6R^7)_n$(5-6 membered heterocyclic), wherein said C_6-C_{10} aryl or 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

R^5 is oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN, and 4-10 membered heterocyclic substituted with R^5;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl;

R^8 is hydrogen or C_1-C_6 alkyl;

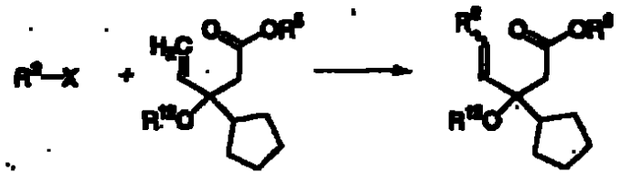
R^{12} is hydrogen or $-C(O)R^{13}$;

R^{13} is C_1-C_6 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, $-OH$, $-OCH_3$, and $-N(C_1$-C_6 alkyl$)_2$; and

n is 0, 1, 2, 3, 4, or 5;

said method comprising:

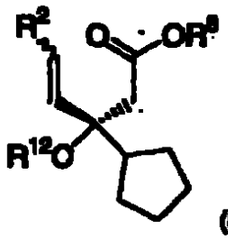
a) treating a compound of formula (6), wherein R^8 is as hereinbefore defined and X is halogen or $-OSO_2CF_3$, with a compound of formula (7) in the presence of a catalyst, wherein R^8 is as hereinbefore defined,



(6) (7) (8)

to afford the compound of formula (8).

Also afforded herein are methods of preparing compounds of formula (8a),



(8a)

wherein:

R^2 is $-(CR^6R^7)_n$-C_6-C_{10} aryl or $-(CR^6R^7)_n$-(5-6 membered heterocyclic), wherein said C_6-C_{10} aryl or 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, $-CN$, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein said C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl groups are optionally substituted with at least one R^5;

R^5 is oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, $-CN$, and 4-10 membered heterocyclic substituted with R^6;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl;

R^9 is hydrogen or C_1-C_6 alkyl;

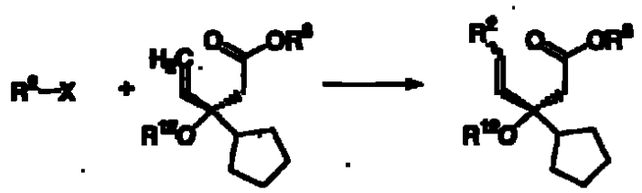
R^{12} is hydrogen or $-C(O)R^{13}$;

R^{13} is C_1-C_6 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_6 alkyl$)_2$; and

n is 0, 1, 2, 3, 4, or 5;

said method comprising:

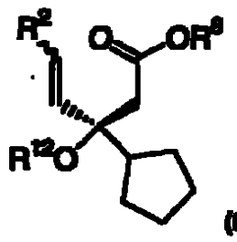
a) *treating a compound of formula* (5), wherein R^2 is as hereinbefore defined and X is halogen, $-OSO_2CF_3$, with a compound of formula (7a) in the presence of a catalyst, wherein R^9 is as hereinbefore defined,



(5) (7a) (8a)

to afford the compound of formula (8a).

The present invention also affords methods of preparing compounds of formula (8b),



(8b)

wherein:

R^2 is $-(CR^6R^7)_n$-C_6-C_{10} aryl or $-(CR^6R^7)_n$-(5-6 membered heterocyclic), wherein said C_6-C_{10} aryl or 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein said C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl groups are optionally substituted with at least one R^5;

R^5 is oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN, and 4-10 membered heterocyclic substituted with R^5;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl;

R^5 is hydrogen or C_1-C_8 alkyl;

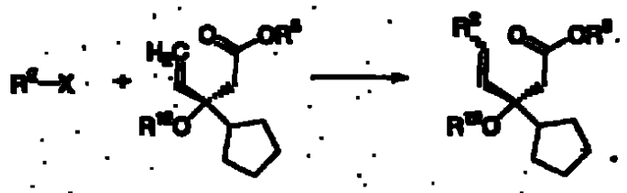
R^{12} is hydrogen or $-C(O)R^{13}$;

R^{13} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$; and

n is 0, 1, 2, 3, 4, or 5;

said method comprising:

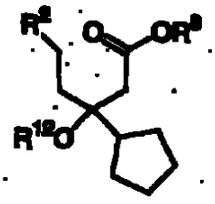
a) treating a compound of formula (6), wherein R^5 is as hereinbefore defined and X is halogen or $-OSO_2CF_3$, with a compound of formula (7b) in the presence of a catalyst, wherein R^5 is as hereinbefore defined,



(6) (7b) (8b)

to afford the compound of formula (8a).

Further provided herein are methods of preparing a compound of formula (9),



(9)

wherein:

R^2 is $-(CR^6R^7)_n$-C_6-C_{10} aryl or $-(CR^6R^7)_n$-(5-6 membered heterocyclic), wherein said C_6-C_{10} aryl or 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

R^5 is oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN, and 4-10 membered heterocyclic substituted with R^6;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl;

R^9 is hydrogen or C_1-C_6 alkyl;

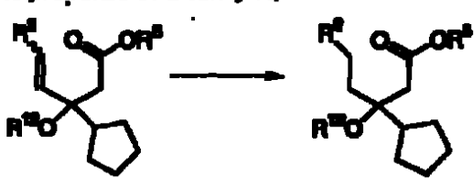
R^{10} is hydrogen or $-C(O)R^{12}$;

R^{12} is C_1-C_6 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_6 alkyl$)_2$; and

n is 0, 1, 2, 3, 4, or 5;

said method comprising:

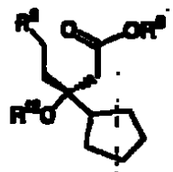
a) treating a compound of formula (8), wherein R^2 and R^9 are as defined herein, with a reducing agent in the presence of a catalyst,



(8) (9)

to afford the compound of formula (9).

Further provided herein are methods of preparing compounds of formula (9a),



(9a)

wherein:

R^2 is $-(CR^6R^7)_n$-C_6-C_{10} aryl or $-(CR^6R^7)_n$-(5-6 membered heterocyclic), wherein said C_6-C_{10} aryl or 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein said C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl groups are optionally substituted with at least one R^5;

R^5 is oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN, and 4-10 membered heterocyclic substituted with R^5;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl;

R^9 is hydrogen or C_1-C_6 alkyl;

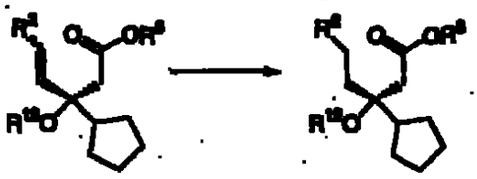
R^{12} is hydrogen or $-C(O)R^{12}$;

R^{12} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$; and

n is 0, 1, 2, 3, 4, or 5;

said method comprising:

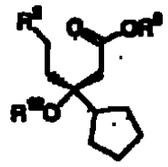
a) treating a compound of formula (9a), wherein R^5 and R^6 are as defined herein, with a reducing agent in the presence of a catalyst,



(9a) (9b)

to afford the compound of formula (9b).

Further provided herein are methods of preparing compounds of formula (9b),



(9b)

wherein:

R^2 is $-(CR^6R^7)_n$-C_6-C_{10} aryl or $-(CR^6R^7)_n$-(5-6 membered heterocyclic), wherein said C_6-C_{10} aryl or 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

R^5 is oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN, and 4-10 membered heterocyclic substituted with R^6;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl;

R^8 is hydrogen or C_1-C_8 alkyl;

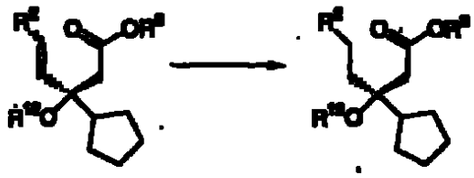
R^{10} is hydrogen or $-C(O)R^{12}$;

R^{12} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$; and

n is 0, 1, 2, 3, 4, or 5;

said method comprising:

a) treating a compound of formula (9b), wherein R^2 and R^8 are as defined herein, with a reducing agent in the presence of a catalyst,

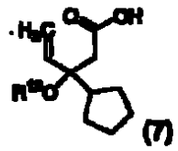


(9b) (9b)

to afford the compound of formula (9b).

Further provided are such methods, wherein said catalyst is selected from palladium and platinum, and such methods wherein said reducing agent is hydrogen. Further provided are such methods, wherein said reducing agent is hydrogen and said catalyst is selected from palladium and platinum.

Also provided herein are methods of preparing stereoisomerically enriched compounds of formula (7),



(7)

wherein:

R^{12} is hydrogen or $-C(O)R^{13}$; and

R^{13} is C_1-C_6 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, $-OH$, $-OCH_3$, and $-N(C_1$-C_6 alkyl$)_2$;

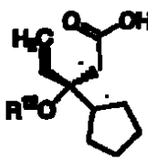
said method comprising:

a) treating a compound of formula (7) with a chiral, non-racemic base to afford a mixture of diastereomeric salts;

b) separating said diastereomeric salts from each other to afford a stereoisomerically enriched diastereomeric salt; and

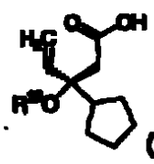
c) converting said stereoisomerically enriched diastereomeric salt into a stereoisomerically enriched compound of formula (7).

Further provided herein are such methods, wherein said stereoisomerically enriched compound of formula (7) is (7a).



(7a)

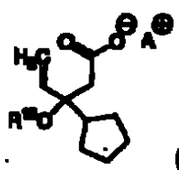
or is a compound of formula (7b),



(7b).

In still another aspect are such above-described methods, wherein said chiral, non-racemic base is a chiral, non-racemic amine. Further provided are such methods wherein said chiral, non-racemic amine is selected from one enantiomer of 1,2,3,4-tetrahydro-1-napthylamine, 1,2,3,4-tetrahydro-1-napthylamine, 1-(2-napthyl)ethylamine, 1-(2-napthyl)ethylamine, and norephedrine. Additionally provided are such methods, wherein said chiral, non-racemic amine is (S)-1,2,3,4-tetrahydro-1-napthylamine.

Further provided herein are compounds of formula (7c),



(7c)

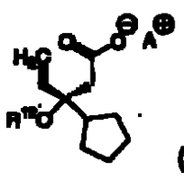
wherein:

R^{12} is hydrogen or $-C(O)R^{13}$;

R^{13} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$; and

A is a suitable counter-ion.

In an additional aspect of the present invention are provided compounds of formula (7d),



(7d)

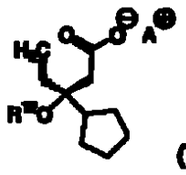
wherein:

R^{12} is hydrogen or $-C(O)R^{13}$;

R^{12} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$; and

A is a suitable counter-ion.

Further provided herein are compounds of formula (7e),



(7e)

wherein:

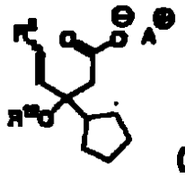
R^{22} is hydrogen or $-C(O)R^{15}$;

R^{23} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$; and

A is a suitable counter-ion.

In still another aspect of the present invention are provided compounds of formula (7c), (7d), and (7e), wherein said suitable counter-ion is derived from an amine. Also provided are such compounds, wherein said amine is chiral, non-racemic amine. Further provided are such compounds wherein said chiral, non-racemic amine is selected from one enantiomer of 1,2,3,4-tetrahydro-1-napthylamine, 1,2,3,4-tetrahydro-1-napthylamine, 1-(2-napthyl)ethylamine, norephedrine, norephedrine. Additionally provided are such methods, wherein said chiral, non-racemic amine is (S)-1,2,3,4-tetrahydro-1-napthylamine.

Also provided herein are compounds of formula (8c)



(8c)

wherein:

R^2 is $-(CR^6R^7)_n$$C_6$-$C_{10}$ aryl or $-(CR^6R^7)_n$(5-6 membered heterocyclic), wherein said C_6-C_{10} aryl or 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$,

$-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

R^5 is oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN, and 4-10 membered heterocyclic substituted with R^6;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl;

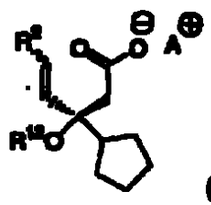
R^{12} is hydrogen or $-C(O)R^{13}$;

R^{13} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$;

n is 0, 1, 2, 3, 4, or 5; and

A is a suitable counter-ion.

The present invention further provides compounds of formula (8d)



(8d)

wherein:

R^4 is $-(CR^6R^7)_n$$C_6$-$C_{10}$ aryl or $-(CR^6R^7)_n$(5-6 membered heterocyclic), wherein said C_6-C_{10} aryl or 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

R^5 is oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN, and 4-10 membered heterocyclic substituted with R^6;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl;

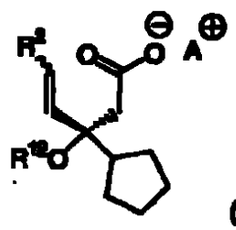
R^{12} is hydrogen or $-C(O)R^{13}$;

R^{13} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$;

n is 0, 1, 2, 3, 4, or 5; and

A is a suitable counter-ion.

Also provided herein are compounds of formula (8e)



(8e)

wherein:

R^2 is $-(CR^6R^7)_n$-C_6-C_{10} aryl or $-(CR^6R^7)_n$-(5-6 membered heterocyclic), wherein said C_6-C_{10} aryl or 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl groups are optionally substituted with at least one R^5;

R^5 is oxo, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN, and 4-10 membered heterocyclic substituted with R^6;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_8 alkyl;

R^{10} is hydrogen or $-C(O)R^{12}$;

R^{12} is C_1-C_8 alkyl or $-(CH_2)(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$;

n is 0, 1, 2, 3, 4, or 5; and

A is a suitable counter-ion.

Further provided herein are compounds of formula (8c), (8d), and (8e), wherein said suitable counter-ion is derived from an amine. Additionally provided are any of these compounds, wherein the amine is a chiral, non-racemic amine. Further provided are any of these compounds wherein the chiral, non-racemic amine is selected from one enantiomer of 1,2,3,4-tetrahydro-1-naphthylamine, 1-(2-naphthyl)ethylamine, and norephedrine.

As used herein, the terms "comprising" and "including" are used in their open, non-limiting sense.

The term "C_1-C_8 alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched, or cyclic moieties (including fused and bridged bicyclic and spirocyclic moieties), or a combination of the foregoing moieties, and containing from 1-8 carbon atoms. For an alkyl group to have cyclic moieties, the group must have at least three carbon atoms.

A "lower alkyl" is intended to mean an alkyl group having from 1 to 4 carbon atoms in its chain. The term "heteroalkyl" refers to a straight- or branched-chain alkyl group having from 2 to 12 atoms in the chain, one or more of which is a heteroatom selected from S, O, and N. Exemplary heteroalkyls include alkyl ethers, secondary and tertiary amines, alkyl sulfides and the like.

The term "C_2-C_8 alkenyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon double bond wherein alkyl is as defined above and including E and Z isomers of said alkenyl moiety, and having from 2 to 8 carbon atoms.

The term "C_2-C_8 alkynyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon triple bond wherein alkyl is as defined above, and containing from 2-8 carbon atoms.

The term "carbocycle" refers to a saturated, partially saturated, unsaturated, or aromatic, monocyclic or fused or non-fused polycyclic, ring structure having only carbon ring atoms (no heteroatoms, i.e., non-carbon ring atoms). Exemplary carbocycles include cycloalkyl, aryl, and cycloalkyl-aryl groups.

A "C_3-C_{10} cycloalkyl group" is intended to mean a saturated or partially saturated, monocyclic, or fused or spiro polycyclic, ring structure having a total of from 3 to 10 carbon ring atoms (but no heteroatoms). Exemplary cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentanyl, cyclohexyl, cycloheptyl, adamantyl, and like groups.

A "heterocycloalkyl group" is intended to mean a monocyclic, or fused or spiro polycyclic, ring structure that is saturated or partially saturated, and has a total of from 3 to 18 ring atoms, including 1 to 5 heteroatoms selected from nitrogen, oxygen, and sulfur. Illustrative Examples of heterocycloalkyl groups include pyrrolidinyl, tetrahydrofuryl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, aziridinyl, and like groups.

The term "C_6-C_{10} aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl. The term "phenyl" and the symbol "Ph," as used herein, refer to a C_6H_5 group.

The term "4-10 membered heterocyclic", as used herein, unless otherwise indicated, includes aromatic and non-aromatic heterocyclic groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 4-10 atoms in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Furthermore, the sulfur atoms contained in such heterocyclic groups may be oxidized with one or two sulfur atoms. Non-aromatic heterocyclic groups include groups having only 4 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 4

membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5 membered heterocyclic group is thiazolyl and an example of a 10 membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups, as derived from the groups listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-3-yl (C-attached). An example of a heterocyclic group wherein 2 ring carbon atoms are substituted with oxo (=O) moieties is 1,1-dioxo-thiomorpholinyl.

The term "5-6 membered heterocyclic" means aromatic and non-aromatic heterocyclic groups containing one to four heteroatoms each selected from O, S and N, and wherein each heterocyclic group has a total of from 5 to 6 atoms in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. The sulfur atoms contained in such heterocyclic groups may be oxidized with one or two sulfur atoms. Furthermore, any atom in the 5-6 membered heterocyclic group may be substituted with an oxo (=O) group, if such substitution would result in a stable compound. Examples of non-aromatic heterocyclic groups, include, but are not limited to, pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-

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azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups include, but are not limited to, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, quinazolinyl, and quinoxalinyl. The foregoing groups, as derived from the groups listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-3-yl (C-attached). An example of a heterocyclic group wherein 2 ring carbon atoms are substituted with oxo (=O) moieties is 1,1-dioxo-thiomorpholinyl.

A "heteroaryl group" is intended to mean a monocyclic or fused or spiro polycyclic, aromatic ring structure having from 4 to 18 ring atoms, including from 1 to 5 heteroatoms selected from nitrogen, oxygen, and sulfur. Illustrative Examples of heteroaryl groups include pyrrolyl, thienyl, oxazolyl, pyrazolyl, thiazolyl, furyl, pyridinyl, pyrazinyl, triazolyl, tetrazolyl, indolyl, quinolinyl, quinoxalinyl, benzthiazolyl, benzodioxinyl, benzodioxolyl, benzooxazolyl, and the like.

The term "alkoxy", as used herein, unless otherwise indicated, includes O-alkyl groups wherein alkyl is as defined above.

The term "amino" is intended to mean the $-NH_2$ radical.

The terms "halogen" and "halo," as used herein represent fluorine, chlorine, bromine or iodine.

The term "oxo," as used herein, means a group (=O). Such a group may be bonded to either a carbon atom or a heteroatom in the compounds of the present invention, if such substitution will result in a stable compound.

The term "trifluoromethyl," as used herein, is meant to represent a group $-CF_3$.

The term "trifluoromethoxy," as used herein, is meant to represent a group $-OCF_3$.

The term "cyano," as used herein, is meant to represent a group –CN.

The term "substituted" means that the specified group or moiety bears one or more substituents. The term "unsubstituted" means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents.

The term "HCV," as used herein, refers to Hepatitis C virus.

The terms "inhibiting Hepatitis C virus" and "inhibiting Hepatitis C virus replication" mean inhibiting Hepatitis C virus replication either *in vitro* or *in vivo*, such as in a mammal,

such as a human, by contacting the Hepatitis C virus with an HCV-replication inhibiting amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof. Such inhibition may take place *in vivo*, such as in a mammal, such as a human, by administering to the mammal a Hepatitis C virus-inhibiting amount of a compound of the present invention. The amount of a compound of the present invention necessary to inhibit replication of the HCV virus either *in vitro* or *in vivo*, such as in a mammal, such as a human, can be determined using methods known to those of ordinary skill in the art. For example, an amount of a compound of the invention may be administered to a mammal, either alone or as part of a pharmaceutically acceptable formulation. Blood samples may then be withdrawn from the mammal and the amount of Hepatitis C virus in the sample may be quantified using methods known to those of ordinary skill in the art. A reduction in the amount of Hepatitis C virus in the sample compared to the amount found in the blood before administration of a compound of the invention would represent inhibition of the replication of Hepatitis C virus in the mammal. The administration of a compound of the invention to the mammal may be in the form of single dose or a series of doses over successive days.

An "HCV-inhibiting agent" means a compound of the present invention or a pharmaceutically acceptable salt or solvate thereof.

The term "HCV-inhibiting amount," as used herein, refers to an amount of a compound of the present invention that is sufficient to inhibit the replication of the Hepatitis C virus when administered to a mammal, such as a human.

The term "HCV polymerase-inhibiting amount," as used herein, means an amount of a compound of the present invention that is sufficient to inhibit the function of the Hepatitis C virus polymerase enzyme when the compound is placed in contact with the enzyme.

A "solvate" is intended to mean a pharmaceutically acceptable solvate form of a specified compound that retains the biological effectiveness of such compound. Examples of solvates include compounds of the invention in combination with solvents such as, but not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, or ethanolamine. A "pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of the specified derivative and that is not biologically or otherwise undesirable. Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates,

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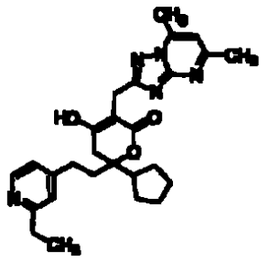
methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycollates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

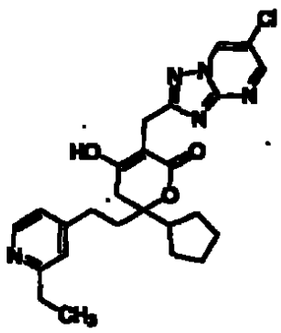
The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups, which may be present in the compounds of the present invention. The compounds of the present invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of the present invention are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the acetate, benzenesulfonate, benzoate, bisorbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, ethylsuccinate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodode, and valerate salts.

The phrases "therapeutically effective amount," "effective amount," and "HCV-inhibiting amount," are intended to mean the amount of an inventive agent that, when administered to a mammal in need of treatment, is sufficient to effect treatment for injury or disease conditions alleviated by the inhibition of HCV RNA replication such as for potentiation of anti-cancer therapies, inhibition of neurotoxicity consequent to stroke, head trauma, and neurodegenerative diseases. The amount of a given HCV-inhibiting agent used in the method of the invention that will be therapeutically effective will very depending upon factors such as the particular HCV-inhibiting agent, the disease condition and the severity thereof, the identity and characteristics of the mammal in need thereof, which amount may be routinely determined by artisans.

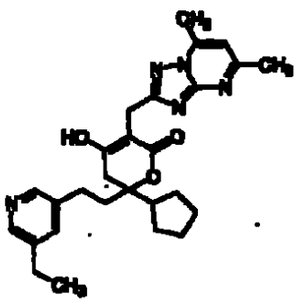
The term "6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one," as used herein, means a chemical compound with the structure:



As used herein, the term "3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one" means a chemical compound with the structure:



The term "6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethylpyridin-3-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one," as used herein, means a chemical compound with the structure:



The term "treating," as used herein, refers to a chemical process or processes in which two or more reactants are allowed to come into contact with each other to effect a chemical change or transformation. For example, when reactant A and reactant B are allowed

to come into contact with each other to afford a new chemical compound(s) C, A is said to have "reacted" with B to produce C.

As used herein, the term "catalyst" means a chemical element or compound that increases the rate of a chemical reaction by reducing the activation energy, but which is left unchanged by the reaction. Examples of catalysts include, but are not limited to, palladium (0) and platinum (0). It is specifically contemplated herein that such catalysts may be formed *in situ* during the course of a chemical reaction, from a so-called "pre-catalyst," but may never actually be observed or isolated. Such pre-catalysts are chemical compounds that are capable of being converted *in situ* during the course of a chemical reaction to a chemically and catalytically competent element or compound. Examples of suitable pre-catalysts include, but are not limited to, $PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(OH)_2$, $Pd(PPh_3)_4$, $Pt(OH)_2$, and $PtCl_2$.

The term "reducing agent," as used herein, means a chemical element or compound that provides electrons for another chemical element or compound in a reaction mixture. Alternatively, it means a chemical element or compound that is capable of affording a saturated chemical compound from an unsaturated chemical compound by the addition of hydrogen. For example, the addition of hydrogen to an alkene of the present invention to afford a saturated alkane is termed "reduction." A reducing agent is a chemical element or compound that is capable of effecting such a reduction, usually in the presence of a catalyst. Examples of reducing agents include, but are not limited to hydrogen, formic acid, and formic acid salts, such as ammonium formate.

The term "protecting," as used herein, refers to a process in which a functional group in a chemical compound is selectively masked by a non-reactive functional group in order to allow a selective reaction(s) to occur elsewhere on said chemical compound. Such non-reactive functional groups are herein termed "protecting groups." For example, the term "hydroxyl protecting group," as used herein refers to those groups that are capable of selectively masking the reactivity of a hydroxyl (-OH) group. The term "suitable protecting group," as used herein refers to those protecting groups that are useful in the preparation of the compounds of the present invention. Such groups are generally able to be selectively introduced and removed using mild reaction conditions that do not interfere with other portions of the subject compounds. Protecting groups that are suitable for use in the processes and methods of the present invention are known to those of ordinary skill in the art. The chemical properties of such protecting groups, methods for their introduction, and their removal can be found, for example, in T. Greene and P. Wuts, *Protective Groups in Organic Synthesis* (3rd ed.), John Wiley & Sons, NY (1999). The terms "deprotecting," "deprotected," or "deprotect,"

as used herein, are meant to refer to the process of removing a protecting group from a compound.

The terms "hydrolyze," "hydrolyzing," "hydrolysis," and "hydrolyzed," as used herein, all mean and refer to a chemical reaction in which an ester, an amide, or both are converted into their corresponding carboxylic acid derivatives, usually through the action of hydroxyl anion (-O-H), such as would be present in a basic, aqueous solution.

The term "leaving group," as used herein, refers to a chemical functional group that generally allows a nucleophilic substitution reaction to take place at the atom to which it is attached. For example, in acid chlorides of the formula Cl-C(O)R, wherein R is alkyl, aryl, or heterocyclic, the –Cl group is generally referred to as a leaving group because it allows nucleophilic substitution reactions to take place at the carbonyl carbon to which it is attached. Suitable leaving groups are known to those of ordinary skill in the art and can include halides, aromatic heterocycles, cyano, amino groups (generally under acidic conditions), ammonium groups, alkoxide groups, carbonate groups, formates, and hydroxy groups that have been activated by reaction with compounds such as carbodiimides. For example, suitable leaving groups can include, but are not limited to, chloride, bromide, iodide, cyano, imidazole, and hydroxy groups that have been allowed to react with a carbodiimide such as dicyclohexylcarbodiimide (optionally in the presence of an additive such as hydroxybenzotriazole) or a carbodiimide derivative.

The term "combination of reagents," means a chemical reagent, or more than one reagent when necessary, that can be used to affect a desired chemical reaction. The choice of a particular reagent, or combination or reagents, will depend on factors that are familiar to those of ordinary skill in the art and include, but are not limited to, the identity of the reactants, the presence of other functional groups in the reactants, the solvent or solvents used in a particular chemical reaction, the temperature at which the chemical reaction will be performed, and the method or methods of purification of the desired chemical reaction product. The choice of a reagent, or combination of reagents, required to affect a particular chemical reaction are within the knowledge of one of ordinary skill in the art and such a choice can be made without undue experimentation.

The term "base," as used herein, means a so-called Bronsted-Lowry base. A Bronsted-Lowry base is a reagent that is capable of accepting a proton (H^+) from an acid present in a reaction mixture. Examples of Bronsted-Lowry bases include, but are not limited to, inorganic bases such as sodium carbonate, sodium bicarbonate, sodium hydroxide, potassium carbonate, potassium bicarbonate, potassium hydroxide, and cesium carbonate, inorganic bases such as triethylamine, diisopropylethylamine, diisopropylamine,

dicyclohexylamine, morpholine, pyrrolidone, piperidine, pyridine, 4-N,N-dimethylaminopyridine (DMAP), and imidazole.

The term "chiral, non-racemic base," as used herein, means a basic compound that can exist in an enantiomeric form and is not present in an equal amount with its corresponding opposite enantiomer. For example, the compound 2-phenylglycinol exists as two enantiomers of opposite configuration, the so-called (R)- and (S)-enantiomers. If the (R)- and the (S)-enantiomers are present in equal amounts, such a mixture is said to be "racemic." If, however, one enantiomer is present in an amount greater than the other, the mixture is said to be "non-racemic."

The term "stereoisomers" refers to compounds that have identical chemical constitution, but differ with regard to the arrangement of their atoms or groups in space. In particular, the term "enantiomers" refers to two stereoisomers of a compound that are non-superimposable mirror images of one another. The terms "racemic" or "racemic mixture," as used herein, refer to a 1:1 mixture of enantiomers of a particular compound. The term "diastereomers", on the other hand, refers to the relationship between a pair of stereoisomers that comprise two or more asymmetric centers and are not mirror images of one another.

The term "stereochemically-enriched" product, when used herein, refers to a reaction product wherein a particular stereoisomer is present in a statistically significant greater amount relative to the other possible stereoisomeric products. For example, a product that comprises more of one enantiomer than the other would constitute a stereochemically enriched product. Similarly, a product that comprises more of one diastereoisomer than others would also constitute a stereochemically enriched product. The methods and processes contained herein are said to afford a "stereochemically enriched" product. In such cases, the methods and processes contained herein begin with a mixture of stereoisomeric compounds in which all possible stereoisomers are present in about an equal amount and afford a product in which at least one stereoisomer is present in a statistically significant greater amount than the others.

The term "diastereomeric," as used herein refers to the relationship between a pair of stereoisomers that comprise two or more asymmetric centers and are non-superimposable mirror images of one another. The phrases "diastereomeric salt," or "diastereomeric salts," as used herein means a salt of a diastereomeric compound, wherein "diastereomer" is as defined herein.

The term "racemic," as used herein, means a composition comprising a 1:1 ratio of enantiomers. The term "scalemic," as used herein, means a composition comprising an unequal amount of enantiomers. For example, a composition comprising a 1:1 mixture of the

(R)- and (S)-enantiomers of a compound of the present invention is termed a racemic composition or mixture. As an additional example, a composition comprising a 2:1 mixture of (R)- and (S)-enantiomers of a compound of the present invention is termed a scalemic composition or mixture. It is specifically contemplated that the methods of the present invention may be advantageously used to prepare a scalemic compound of the present invention from a racemic compound of the present invention.

The terms "resolution" and "resolving" mean a method of physically separating stereoisomeric compounds from a mixture of stereoisomers, such as a racemic mixture comprising two enantiomers of a particular compound. As used herein, "resolution" and "resolving" are meant to include both partial and complete resolution.

The terms "separating" or "separated," as used herein, mean a process of physically isolating at least two different chemical compounds from each other. For example, if a chemical reaction takes place and produces at least two products, (A) and (B), the process of isolating both (A) and (B) from each other is termed "separating" (A) and (B). It is specifically contemplated that the separations of the present invention may be partial or complete as determined by analytical techniques known to those of ordinary skill in the art and those described herein.

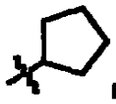
The term "converting," as used herein, means allowing a chemical reaction to take place with a starting material or materials to produce a different chemical product. For example, if chemical reactants (A) and (B) are allowed to react with each other to produce product (C), starting materials (A) and (B) can be said to have "converted" to product (C), or it can be said that (A) was "converted" to (C), or that (B) was "converted" to (C).

The term "suitable counter-ion," as used herein, means an ion or ions opposite in charge to the ion present in the compound or compounds of the invention such that the overall complex or salt has a neutral charge. For example, if the compound of the present invention contains an overall negative one (-1) charge, a suitable counter ion would be one with an overall positive one (+1) charge that would afford an overall neutral charge for the complex or salt. Examples of suitable positive (+) counter-ions include, but are not limited to, sodium ion (Na^+), potassium ion (K^+), cesium ion (Cs^+), and protonated amines (such as protonated triethylamine, protonated dicyclohexylamine, protonated morpholine, or protonated pyridine). Alternatively, if the compound of the invention contains an overall positive one (+1) charge, a suitable counter-ion would be one with an overall negative one (-1) charge that would afford an overall neutral charge for the complex or salt. Examples of suitable negative (-) counter-ions include, but are not limited to, fluoride (F^-), chloride (Cl^-), bromide (Br^-), iodide (I^-), hydroxide (^-OH), and acetate ($^-O\text{-}C(O)CH_3$). It is also possible that the suitable counter-ion is

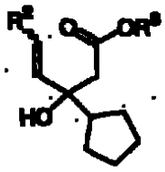
the compounds of the present invention, including the compounds used in the methods of the present invention, may have more than a single charge associated with them. For example, if the compound of the invention contains a negative one (-1) charge, the suitable counter-ion may contain a plus two (+2) charge, such that two compounds of the invention with negative one charges are associated with one suitable counter-ion. Examples of suitable counter-ions with more than one positive charge include, but are not limited to calcium (Ca^{2+}). Finally, it is also contemplated that the compounds of the present invention may contain more than one charge, such that more than one suitable counter-ion may be required to afford an overall neutral complex or salt. For example, the compound of the present invention may contain more than one negative one (-1) charges, such that two suitable counter-ions, each with a plus one (+1) charge, are required to afford an overall neutral complex or salt.

The term "substituted," means that the specified group or moiety bears one or more substituents. The term "unsubstituted," means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents.

Detailed Description

In accordance with a convention used in the art, the symbol  is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure. In accordance with another convention, in some structural formulas herein the carbon atoms and their bound hydrogen atoms are not explicitly depicted, e.g.,  represents a methyl group,  represents an ethyl group,  represents a cyclopentyl group, etc.

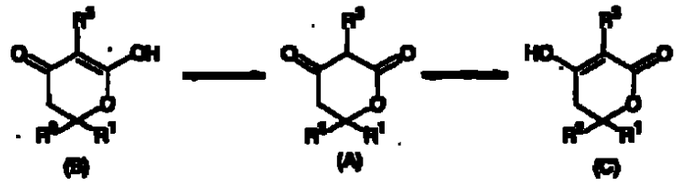
With respect to compounds of the invention that are alkenes, the symbol "∿∿∿" denotes that either the E- or Z-isomer, or mixtures of the E- and Z-isomers, may be present. For example, in the structural depiction, the use of the symbol "∿∿∿" for the bond from the R^2 group to the alkene,



82
83

denotes that either the E- or Z-isomer, or mixtures of the E- and Z-isomers, are meant to be represented.

The compounds of the present invention may exist in several tautomeric forms. For example, a compound of the invention may exist in a form in which two ketones are present on a ring of the compound, as shown in (A) below. Alternatively, the compounds of the present invention may exist in at least two different enol forms, as shown in compounds (B) and (C) below. These three forms may be in equilibrium and the compounds of the invention may exist in more than one of these forms at the same time. For example, in a particular compound of the invention, a certain percentage of the molecules may be present in form (A) while the remainder are present in form (B) or form (C). Which form predominates in a particular compound of the invention depends on several factors that include, but are not limited to, whether the compound is in solid, liquid, or crystalline form, whether the compound is dissolved in a solvent and the identity of the solvent, the environmental temperature, and the relative humidity. It is specifically contemplated that when the compounds of the present invention are drawn in a particular form, form (A) for example, all the tautomeric forms, forms (B) and (C) for example, are included as well.



The compounds of the present invention may have asymmetric carbon atoms. The carbon-carbon bonds of the compounds of the present invention may be depicted herein using a solid line (———), a solid wedge (▬▬), or a dotted wedge (▬▬). The use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers at that carbon atom are included. The use of either a solid or dotted wedge to depict bonds to asymmetric carbon atoms is meant to indicate that only the stereoisomer shown is meant to be included. It is possible that compounds of the invention may contain more than one asymmetric carbon atom. In those compounds, the use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers are meant to be included. The use of a solid line to depict bonds to one or more asymmetric carbon atoms in a compound of the invention and the use of a solid or dotted wedge to depict bonds to other asymmetric carbon atoms in the same compound is meant to indicate that a mixture of diastereomers is present.

Solutions of individual stereoisomeric compounds of the present invention may rotate plane-polarized light. The use of either a "(+)" or "(-)" symbol in the name of a compound of the invention indicates that a solution of a particular stereoisomer rotates plane-polarized light in the (+) or (-) direction, as measured using techniques known to those of ordinary skill in the art.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixtures into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. All such isomers, including diastereomeric mixtures and pure enantiomers are considered as part of the invention.

Alternatively, individual stereoisomeric compounds of the present invention may be prepared in enantiomerically enriched form by asymmetric synthesis. Asymmetric synthesis may be performed using techniques known to those of skill in the art, such as the use of asymmetric starting materials that are commercially available or readily prepared using methods known to those of ordinary skill in the art, the use of asymmetric auxiliaries that may be removed at the completion of the synthesis, or the resolution of intermediate compounds using enzymatic methods. The choice of such a method will depend on factors that include, but are not limited to, the availability of starting materials, the relative efficiency of a method, and whether such methods are useful for the compounds of the invention containing particular functional groups. Such choices are within the knowledge of one of ordinary skill in the art.

When the compounds of the present invention contain asymmetric carbon atoms, the derivative salts, prodrugs and solvates may exist as single stereoisomers, racemates, and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates, and mixtures thereof are intended to be within the scope of the present invention.

As generally understood by those skilled in the art, an optically pure compound is one that is enantiomerically pure. As used herein, the term "optically pure" is intended to mean a compound comprising at least a sufficient activity. Preferably, an optically pure amount of a single enantiomer to yield a compound having the desired pharmacological pure compound of the invention comprises at least 90% of a single isomer (80% enantiomeric excess), more preferably at least 95% (90% e.e.), even more preferably at least 97.5% (95% e.e.), and most preferably at least 99% (98% e.e.).

If a derivative used in the method of the invention is a base, a desired salt may be prepared by any suitable method known to the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid; hydrobromic acid; sulfuric acid; nitric acid; phosphoric acid; and the like, or with an organic acid, such as acetic acid; maleic acid; succinic acid; mandelic acid; fumaric acid; malonic acid; pyruvic acid; oxalic acid; glycolic acid; salicylic acid; pyranosidyl acid, such as glucuronic acid or galacturonic acid; alpha-hydroxy acid, such as citric acid or tartaric acid; amino acid, such as aspartic acid or glutamic acid; aromatic acid, such as benzoic acid or cinnamic acid; sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid; and the like.

If a derivative used in the method of the invention is an acid, a desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary); an alkali metal or alkaline earth metal hydroxide; or the like. Illustrative Examples of suitable salts include organic salts derived from amino acids such as glycine and arginine; ammonia; primary, secondary, and tertiary amines; and cyclic amines, such as piperidine, morpholine, and piperazine; as well as inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

In the case of derivatives, prodrugs, salts, or solvates that are solids, it is understood by those skilled in the art that the derivatives, prodrugs, salts, and solvates used in the method of the invention, may exist in different polymorph or crystal forms, all of which are intended to be within the scope of the present invention and specified formulas. In addition, the derivative, salts, prodrugs and solvates used in the method of the invention may exist as tautomers, all of which are intended to be within the broad scope of the present invention.

The compounds of the present invention that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The desired acid salt can also be precipitated from a

solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid.

Those compounds of the present invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of the present invention. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The activity of the compounds as inhibitors of HCV activity may be measured by any of the suitable methods available in the art, including *in vivo* and *in vitro* assays. An Example of a suitable assay for activity measurements is the HCV replicon assay described herein.

Administration of the compounds and their pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates may be performed according to any of the accepted modes of administration available to those skilled in the art. Illustrative Examples of suitable modes of administration include oral, nasal, parenteral, topical, transdermal, and rectal. Oral and intravenous deliveries are preferred.

An HCV-inhibiting agent of the present invention may be administered as a pharmaceutical composition in any suitable pharmaceutical form. Suitable pharmaceutical forms include solid, semisolid, liquid, or lyophilized formulations, such as tablets, powders, capsules, suppositories, suspensions, liposomes, and aerosols. The HCV-inhibiting agent may be prepared as a solution using any of a variety of methodologies. For Example, the HCV-inhibiting agent can be dissolved with acid (e.g., 1 M HCl) and diluted with a sufficient volume of a solution of 5% dextrose in water (D5W) to yield the desired final concentration of HCV-inhibiting agent (e.g., about 15 mM). Alternatively, a solution of D5W containing about 15 mM HCl can be used to provide a solution of the HCV-inhibiting agent at the appropriate

concentration. Further, the HCV-inhibiting agent can be prepared as a suspension using, for example, a 1% solution of carboxymethylcellulose (CMC).

Acceptable methods of preparing suitable pharmaceutical forms of the pharmaceutical compositions are known or may be routinely determined by those skilled in the art. For Example, pharmaceutical preparations may be prepared following conventional techniques of the pharmaceutical chemist involving steps such as mixing, granulating, and compressing when necessary for tablet forms, or mixing, filling, and dissolving the ingredients as appropriate, to give the desired products for oral, parenteral, topical, intravaginal, intranasal, intrabronchial, intraocular, intraaural, and/or rectal administration.

Pharmaceutical compositions of the invention may also include suitable excipients, diluents, vehicles, and carriers, as well as other pharmaceutically active agents, depending upon the intended use. Solid or liquid pharmaceutically acceptable carriers, diluents, vehicles, or excipients may be employed in the pharmaceutical compositions. Illustrative solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, pectin, acacia, magnesium stearate, and stearic acid. Illustrative liquid carriers include syrup, peanut oil, olive oil, saline solution, and water. The carrier or diluent may include a suitable prolonged-release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. When a liquid carrier is used, the preparation may be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid (e.g., solution), or a nonaqueous or aqueous liquid suspension.

A dose of the pharmaceutical composition may contain at least a therapeutically effective amount of an HCV-inhibiting agent and preferably is made up of one or more pharmaceutical dosage units. The selected dose may be administered to a mammal, for example, a human, in need of treatment mediated by inhibition of HCV activity, by any known or suitable method of administering the dose, including topically, for example, as an ointment or cream; orally; rectally, for example, as a suppository; parenterally by injection; intravenously; or continuously by intravaginal, intranasal, intrabronchial, intraaural, or intraocular infusion. When the composition is administered in conjunction with a cytotoxic drug, the composition can be administered before, with, and/or after introduction of the cytotoxic drug. However, when the composition is administered in conjunction with radiotherapy, the composition is preferably introduced before radiotherapy is commenced.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Ed. (1975).

It will be appreciated that the actual dosages of the HCV-inhibiting agents used in the pharmaceutical compositions of this invention will be selected according to the properties of the particular agent being used, the particular composition formulated, the mode of administration and the particular site, and the host and condition being treated. Optimal dosages for a given set of conditions can be ascertained by those skilled in the art using conventional dosage-determination tests. For oral administration, e.g., a dose that may be employed is from about 0.001 to about 1000 mg/kg body weight, or from about 0.1 to about 100 mg/kg body weight, or from about 1 to about 50 mg/kg body weight, or from about 0.1 to about 1 mg/kg body weight, with courses of treatment repeated at appropriate intervals. The dosage forms of the pharmaceutical formulations described herein may contain an amount of a compound of the present invention, or a pharmaceutically acceptable salt of solvate thereof, deemed appropriate by one of ordinary skill in the art. For example, such dosage forms may contain from about 1 mg to about 1500 mg of a compound of the present invention, or may contain from about 5 mg to about 1500 mg, or from about 5 mg to about 1250 mg, or from about 10 mg to about 1250 mg, or from about 25 mg to about 1250 mg, or from about 25 mg to about 1000 mg, or from about 50 mg to about 1000 mg, or from about 50 mg to about 750 mg, or from about 75 mg to about 750 mg, or from about 100 mg to about 750 mg, or from about 125 mg to about 750 mg, or from about 150 mg to about 750 mg, or from about 150 mg to about 500 mg of a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof.

The subject invention also includes isotopically-labelled compounds, which are identical to those recited in the compounds of the present invention, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced

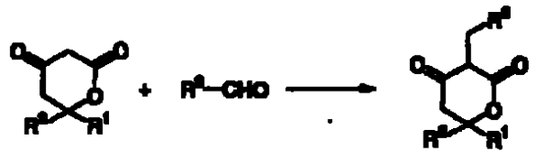
dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of the present invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

The compounds of the present invention are potent inhibitors of Hepatitis C virus, in particular HCV replication, and even in more particular, HCV RNA-dependent RNA-polymerase. The compounds are all adapted to therapeutic use as anti-HCV agents in mammals, particularly in humans.

The active compound may be applied as a sole therapy or may involve one or more other antiviral substances, for example those selected from, for example, HCV inhibitors such as interferon alphacon-1, natural interferon, interferon beta-1a, interferon omega, interferon gamma-1b, interleukin-10, BILN 2061 (serine protease), amantadine (Symmetrel), thymosine alpha-1, ribamidine; HIV inhibitors such as nelfinavir, delavirdine, indinavir, nevirapine, saquinavir, and lamivudine. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment.

In general, the compounds of the present invention may be prepared according to the methods described herein as well as methods known to those of ordinary skill in the art. The methods described herein are not meant to, and should not be construed to, limit the scope of the present invention in any way.

The compounds of formula (4) may be prepared by reaction of a compound of formula (11), wherein R^1 and R^2 are as hereinbefore defined, with a compound of formula (12), wherein R^3 is as hereinbefore defined.



(11) (12) (4)

These reactions are generally performed in the presence of a reducing agent, such as a borane source or hydrogen in the presence of suitable catalyst. Suitable borane sources include, but are not limited to, borane-trimethylamine complex, borane-dimethylamine complex, borane t-butyl amine complex, and borane-pyridine complex. Suitable catalysts for use in the presence of a reducing agent such as hydrogen include, but are not limited to, nickel, palladium, rhodium and ruthenium. Furthermore, such reactions are performed in a solvent or mixture of solvents that will not interfere with desired chemical reaction.

Furthermore, appropriate solvents include those that are known to those of skill in the art to be compatible with the reaction conditions and include alkyl esters and aryl esters, alkyl, heterocyclic, and aryl ethers, hydrocarbons, alkyl and aryl alcohols, alkyl and aryl halogenated compounds, alkyl or aryl nitriles, alkyl and aryl ketones, and non-protic heterocyclic solvents. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent if it will not interfere with the desired transformation. Finally, such reactions can be performed at a temperature in the range of from about 0 °C to about 75 °C, preferably in the range of from about 0 °C to about 32 °C, most preferably at room or ambient temperature. The choice of a particular reducing agent, solvent, and temperature will depend on several factors including, but not limited to, the identity of the particular reactants and the functional groups present in such reactants. Such choices are within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

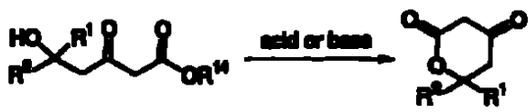
Alternatively, compounds of formula (4) may be prepared by reaction of a compound of formula (11) with a compound of formula (24), wherein X is a suitable leaving group. Suitable leaving groups include, but are not limited to, halides (such as chloride, bromide, and iodide), and activated esters (such as methanesulfonate, trifluoromethane sulfonate, and tosyl esters). Such reactions can be performed in the presence of a suitable base. Suitable bases include, but are not limited to, sodium carbonate, sodium bicarbonate, potassium carbonate, cesium carbonate, sodium hydroxide, potassium hydroxide, sodium hydride, lithium hydride, potassium hydride, and lithium diisopropylamide. Furthermore, appropriate solvents include those that are known to those of skill in the art to be compatible with the reaction conditions and include alkyl, heterocyclic, and aryl ethers, hydrocarbons, alkyl and aryl halogenated compounds, alkyl or aryl nitriles, and non-protic heterocyclic solvents. For example, suitable solvents include, but are not limited to, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, acetonitrile, benzonitrile, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used

as a co-solvent if it will not interfere with the desired transformation. Finally, such reactions can be performed at a temperature in the range of from about 0 °C to about 150 °C, preferably in the range of from about 0 °C to about 32 °C, most preferably at room or ambient temperature. The choice of a particular reducing agent, solvent, and temperature will depend on several factors including, but not limited to, the identity of the particular reactants and the functional groups present in such reactants. Such choices are within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.



(11) (84) (4)

Compounds of formula (11), wherein R^1 and R^2 are as hereinbefore defined, can be prepared from compounds of formula (25), by reaction with a suitable acid or base.



(25) (11)

Suitable bases for use in these reactions include inorganic bases and organic bases. Suitable inorganic bases include, but are not limited to, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, sodium hydride, potassium hydride, and cesium carbonate. Preferably, the base is potassium carbonate. Suitable organic bases include, but are not limited to, pyridine, triethylamine, tributylamine, triethanolamine, N-methylmorpholine, N-ethyl-N,N-diisopropylamine, DBU, and 4-N,N-dimethylaminopyridine. These reactions can also be performed in the presence of a catalytic amount of a suitable acid. Suitable acids include both Bronsted-Lowry and Lewis acids. Furthermore, these reactions are generally performed in a solvent or mixture of solvents that will not interfere with desired chemical reaction. Furthermore, appropriate solvents include those that are known to the skilled in the art to be compatible with the reaction conditions and include alkyl esters and aryl esters, alkyl, heterocyclic, and aryl ethers, hydrocarbons, alkyl and aryl alcohols, alkyl and aryl halogenated compounds, alkyl or aryl nitriles, alkyl and aryl ketones, and non-protic heterocyclic solvents. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether,

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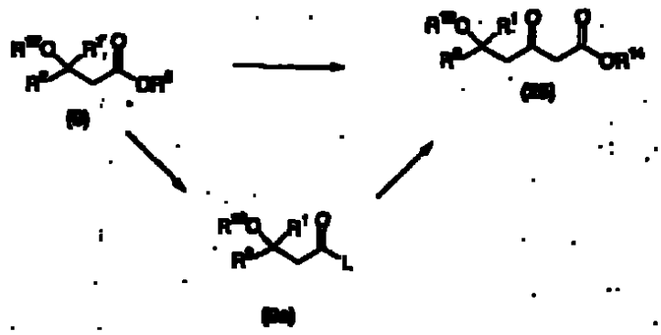
methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent if it will not interfere with the desired transformation. Finally, such reactions can be performed at a temperature in the range of from about 0 °C to about 100 °C, or in the range of from about 25 °C to about 100 °C, or in the range of from about 35 °C to about 75 °C, or in the range of from about 45 °C to about 55 °C, or at about 50 °C. The choice of a particular reducing agent, solvent, and temperature will depend on several factors including, but not limited to, the identity of the particular reactants and the functional groups present in such reactants. Such choices are within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

Alternatively, the compounds of formula (11), wherein R^1 and R^6 are as hereinbefore defined, can be prepared from compounds of formula (25), wherein R^{14} is hydrogen, by reaction with a suitable reagent, or a combination of suitable reagents, to affect cyclization. Such reactions may be performed in the presence of a reagent or combination of reagents that will convert the carboxylic –OH group into a suitable leaving group, such as chlorine or an imidazole group, for example. The term "a suitable leaving group" means a chemical group that is capable of being displaced when a suitable nucleophilic group, such as a hydroxyl group, reacts with the carbonyl carbon in the carboxyl group in the compounds of formula (25). Such suitable leaving groups can be introduced in the compounds of formula (25) wherein R^{14} is hydrogen, by reaction of the compound of formula (25) with a suitable reagent or combination of reagents known to those of ordinary skill in the art. For example, a compound of formula (25), wherein R^{14} is hydrogen, may be allowed to react with phosgene (ClC(O)Cl) or triphosgene ($(Cl)_3C(O)C(Cl)_3$) to afford a so-called acid chloride, that is where the carboxy hydroxyl group has been replaced with a chlorine atom. Furthermore, the compounds of formula (25) may be converted to compounds wherein the carboxy hydroxyl group is replaced by another type of suitable leaving group, such as an imidazole group. Such compounds can be prepared using a suitable reagent or combination of reagents such as carbonyl diimidazole. These types of reactions may be performed in the presence of a suitable base, such as triethylamine for example, and in an aprotic solvent that will not interfere with the desired chemical reaction, chloroform or dichloromethane for example. Furthermore, such reactions may be performed at a temperature in the range from about –78 °C to about 75 °C, or in the range of from about 0 °C to about 50 °C, or from about 0 °C to about 25 °C. The choice of a

suitable reagent to convert the carboxyl group into an acid chloride, for example, a suitable solvent, and a suitable temperature are all choices within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

The compounds of formula (25), wherein the carboxy hydroxyl group has been converted to an appropriate leaving group, an acid chloride for example, may then be converted to compounds of formula (11) by reaction in the presence of a suitable base. Suitable bases include, but are not limited to, inorganic bases and organic bases. Suitable inorganic bases include, but are not limited to, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, and cesium carbonate. Suitable organic bases include, but are not limited to, pyridine and 4-N,N-dimethylaminopyridine. Furthermore, appropriate solvents include those that are known to those of skill in the art to be compatible with the reaction conditions and include alkyl esters and aryl esters, alkyl, heterocyclic, and aryl ethers, hydrocarbons, alkyl and aryl alcohols, alkyl and aryl halogenated compounds, alkyl or aryl nitriles, alkyl and aryl ketones, and non-protic heterocyclic solvents. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. The particular choices of activating agent, solvent, base, and temperature to effect the desired transformation are all choices within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

Compounds of formula (25), wherein R^1 and R^2 are as hereinbefore defined, P^1 is hydrogen or a suitable protecting group, and R^{14} is C_1-C_8 alkyl, -Si(C_1-C_8 alkyl)$_3$, or –CH$_2$(C_6-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen,C_1-C_8 alkyl, -OH, -OCH$_3$, and –N(C_1-C_8 alkyl)$_2$, can be prepared from compounds of formula (9), wherein R^1 and R^2 are as hereinbefore defined, R^{12} is hydrogen or –C(O)R^{13}, and R^{13} is hydrogen, C_1-C_8 alkyl, -Si(C_1-C_8 alkyl)$_3$, or –CH$_2$(C_6-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen,C_1-C_8 alkyl, -OH, -OCH$_3$, and –N(C_1-C_8 alkyl)$_2$, or from compounds of formula (9a), wherein R^1, R^2, and R^{12} are as hereinbefore defined, and L is a suitable leaving group, as shown below.



The compound of formula (9) wherein R^5 is hydrogen may be allowed to react with a reagent or combination of reagents that will convert the carboxy hydroxyl group to a suitable leaving group -OA. Such groups include activated esters, such as various benzoyl esters, such as a 2,6-dinitrobenzoyl ester or a perfluorobenzoyl ester, mixed anhydrides, or an intermediate derived from reaction of the carboxy group with a carbodiimide, such as diethyl carbodiimide or diisopropyl carbodiimide. These intermediate compounds can be prepared by reaction of the carboxy group with a suitable reagent, such as a carbodiimide, in a solvent that will not interfere with the desired chemical reaction, such as chloroform, dichloromethane, or tetrahydrofuran, and at a temperature of from about –78 °C to about 100 °C, or in the range of from about 0 °C to about 75 °C, or in the range of from about 0 °C to about 50 °C. The compound of formula (9) containing the suitable leaving group –OA can be isolated or can be allowed to react in the next step without any further purification. The compound containing the suitable leaving group –OA can then be allowed to react with a reagent or combination of reagents to provide the compound of formula (25). Such suitable reagents include, but are not limited to, malonate anions derived from deprotonation of a malonate derivative with a suitable base, and magnesium malonate esters, such as methyl magnesium malonate and ethyl magnesium malonate. Furthermore, appropriate solvents include those that are known to those of skill in the art to be compatible with the reaction conditions and include alkyl esters and aryl esters, alkyl, heterocyclic, and aryl ethers, hydrocarbons, alkyl and aryl alcohols, alkyl and aryl halogenated compounds, alkyl or aryl nitriles, alkyl and aryl ketones, and non-protic heterocyclic solvents. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone,

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2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Furthermore, they are performed at a temperature in the range of from about 0 °C to about 150 °C, or in the range of from about 0 °C to about 75 °C, or in the range of from about 20 °C to about 75 °C, or in the range of from about 25 °C to about 50 °C, or at about 40 °C. The particular choice of reagent or combination or reagents, solvent or solvents, and temperature are within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

Alternatively, the compounds of formula (25) can be prepared from compounds of formula (9), wherein R^5 is C_1-C_6 alkyl, -Si(C_1-C_6 alkyl)$_3$, or –CH_2(C_6-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, -OH, -OCH_3, and –N(C_1-C_6 alkyl)$_2$, by reaction with a reagent or combination of reagents to provide the compound of formula (III). Such suitable reagents include, but are not limited to magnesium malonate esters, such as methyl magnesium malonate and ethyl magnesium malonate. Such suitable reagents include, but are not limited to, malonate anions derived from deprotonation of a malonate derivative with a suitable base, and magnesium malonate esters, such as methyl magnesium malonate and ethyl magnesium malonate. Furthermore, appropriate solvents include those that are known to those of skill in the art to be compatible with the reaction conditions and include alkyl esters and aryl esters, alkyl, heterocyclic, and aryl ethers, hydrocarbons, alkyl and aryl alcohols, alkyl and aryl halogenated compounds, alkyl or aryl nitriles, alkyl and aryl ketones, and non-protic heterocyclic solvents. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Furthermore, they are performed at a temperature in the range of from about 0 °C to about 150 °C, or in the range of from about 0 °C to about 75 °C, or in the range of from about 20 °C to about 75 °C, or in the range of from about 25 °C to about 50 °C, or at about 40 °C. The particular choice of reagent or combination or reagents, solvent or solvents, and temperature are within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

Additionally, the compounds of formula (25) can be prepared from compounds of formula (9a), wherein R^1, R^2, and R^{10} are as hereinbefore defined, and L is a suitable leaving group, by reaction with a reagent or combination of reagents to provide the compound of formula (25). Suitable leaving groups include, but are not limited to, chloride, bromide, iodide, and imidazole. Compounds with suitable leaving groups can be prepared from compounds of formula (9) wherein R^6 is –OH by reaction with an activating reagent or combination of activating reagents capable of replacing the carboxy hydroxyl group with L. Such activating reagents include, but are not limited to, thionyl chloride ($SOCl_2$), phosgene, triphosgene, and carbonyldiimidazole. These reactions are typically performed in the presence of a base that will not interfere with the desired chemical reaction, such as triethylamine, ethyldiisopropylamine, pyridine, or 4-N,N,-dimethylaminopyridine. Furthermore, the reactions are performed in an aprotic solvent that will not interfere with the desired chemical reaction such as tetrahydrofuran, methylbutyl ether, diisopropyl ether, diethyl ether, toluene, chloroform, dichloromethane, or 1,2-dichloroethane, for example. Furthermore, such reactions are performed at a temperature in the range of from about –78 °C to about 100 °C, or in the range of from about -50 °C to about 100 °C, or in the range of from about 0 °C to about 75 °C, or in the range of from about 0 °C to about 50 °C, or in the range of from about 0 °C to about 25 °C. After conversion of a compound of formula (9) to a compound of formula (9a), the compound of formula (9a) may be allowed to react with a reagent or combination of reagents capable of converting the compound of formula (9a) to one of formula (25). Such suitable reagents include, but are not limited to magnesium malonate esters, such as methyl magnesium malonate and ethyl magnesium malonate. These reactions are performed in a solvent or mixture of solvents that will not interfere with the desired chemical reaction, such as diethyl ether, methyl t-butyl ether, and tetrahydrofuran, or mixtures thereof. Furthermore, they are performed at a temperature in the range of from about 0 °C to about 100 °C, or in the range of from about 0 °C to about 75 °C, or in the range of from about 20 °C to about 75 °C, or in the range of from about 25 °C to about 50 °C, or at about 40 °C. The particular choice of reagent or combination or reagents, solvent or solvents, and temperature are within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

The reaction of compounds of formula (9), (9a), or suitably activated derivatives thereof, with a reagent or combination or reagents to afford a compound of formula (25) may require the introduction of a suitable protecting group for the tertiary hydroxyl group in the compounds of formula (9). Such protecting groups should be capable of being introduced into the compound of formula (9) under conditions that will selectively protect such hydroxyl group. Such reagents and conditions are well-known to those of ordinary skill in the art and can be

found, for example, in T. Greene and P. Wuts, *Protective Groups in Organic Synthesis* (3rd ed.), John Wiley & Sons, NY (1999). For example, a silyl protecting group, such as a triisopropyl silyl group, can be introduced into the compound of formula (9) to selectively protect the tertiary hydroxyl group. Such a group can be introduced using an activated silane reagent, such as triisopropyl silyl chloride for example, in the presence of a base, such as triethylamine for example, and in an aprotic solvent, chloroform for example. The protected compound of formula (9) may then be allowed to react as described above to afford a compound of formula (25) in protected form. The protected compound (25) can then be deprotected using conditions known to those of ordinary skill in the art. For example, if the tertiary hydroxyl group in the compound of formula (25) is protected with as a silyl ether, for example, it can be deprotected using a fluoride source, tetrabutylammonium fluoride for example, in a solvent such as THF and at a temperature in the range of from about 0 °C to about 100 °C, or in the range of from about 0 °C to about 25 °C. Whether the tertiary hydroxyl group in the compound of formula (9) requires protection prior to conversion to the compound of formula (25) is within the knowledge of one of ordinary skill in the art and such a choice can be made without undue experimentation.

Reagents such as magnesium malonate esters, methyl magnesium malonate or ethyl magnesium malonate for example, are either commercially available or can be prepared using methods known to those of ordinary skill in the art. For example, ethyl magnesium malonate can be prepared by reaction of magnesium ethoxide with ethyl malonic acid, as shown below.



Compounds of formula (9), wherein R^1, R^2, and R^{1a}, are as hereinbefore defined, and R^3 is hydrogen, can be prepared from compounds of formula (9),



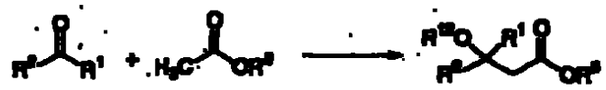
(9)

wherein R^3 is C_1-C_8 alkyl, $-Si(C_1$-C_8 alkyl$)_3$, or $-CH_2(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_8 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_8 alkyl$)_2$, by hydrolysis with a suitable acid or base in an aqueous solvent. Suitable bases include, but are not limited to, lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, and potassium carbonate. Suitable acids include, but are not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, and sulfuric acid. These reactions can be performed in a solvent or mixture of solvents that will not interfere with

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the desired chemical reaction including, but not limited to, diethyl ether, methyl tert-butyl ether, tetrahydrofuran, methyl alcohol, ethyl alcohol, iso-propyl alcohol, n-propyl alcohol, and tert-butyl alcohol. Water may be advantageously used as a co-solvent in these reactions. Furthermore, these reactions are typically performed at a temperature in the range from about −78 °C to about 50 °C, or in the range from about −35 °C to about 50 °C, or in the range of from about −85 °C to about 25 °C.

Compounds of formula (9), wherein R^1, R^2, and R^{10} are as hereinbefore defined, and R^5 is hydrogen, C_1-C_6 alkyl, $-Si(C_1$-C_6 alkyl$)_3$, or $-CH_2(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_6 alkyl$)_2$, can be prepared by reaction of a compound of formula (25), wherein R^1 and R^2 are as hereinbefore defined, with a compound of formula (14), wherein R^5 is hydrogen, C_1-C_6 alkyl, $-Si(C_1$-C_6 alkyl$)_3$, or $-CH_2(C_6$-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, -OH, $-OCH_3$, and $-N(C_1$-C_6 alkyl$)_2$, as shown below.

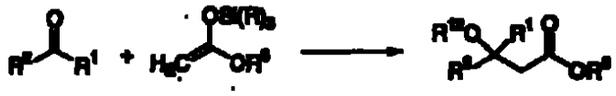


(25) (14) (9)

These reactions can be performed in the presence of strong base to first react with the compound of formula (14) to afford an anion. Suitable strong bases for such reactions include lithium hexamethyl disilylazide (LiHMDS), sodium hexamethyl disilazide, potassium hexamethyl disilazide, lithium diisopropyl amide, and magnesium diisopropylamide. Furthermore, such reactions can be performed in the presence of a solvent that will not interfere with the desired chemical reaction. Suitable solvents include, but are not limited to, neat solutions of the compound of formula (14), diethyl ether, methyl tert-butyl ether, and tetrahydrofuran. Additionally, such reactions can be performed at a temperature in the range of from about −78 °C to about 25 °C, or in the range of from about −60 °C to about 25 °C, or from about −35 °C to about 25 °C, or in the range of from about −35 °C to about 0 °C.

Alternatively, compounds of formula (9) can be prepared by reaction of a compound of formula (25) with a silyiketene acetal as shown below, wherein R is, for example, a C_1-C_6 alkyl group, and R^2 is as hereinbefore defined. These reactions can be performed in the presence of a catalytic or stoichiometric amount of a suitable Lewis acid that include, but are not limited to, aluminum (III) chloride, titanium (II) chloride, titanium (IV) chloride, tin (II) chloride, and tin (IV) chloride. Furthermore, such reactions can be performed in the presence of a solvent that will not interfere with the desired chemical reaction. Suitable solvents include, but are not

limited to, diethyl ether, methyl tert-butyl ether, and tetrahydrofuran. Additionally, such reactions can be performed at a temperature in the range of from about –78 °C to about 25 °C, or in the range of from about –50 °C to about 25 °C, or from about –35 °C to about 25 °C, or in the range of from about –35 °C to about 0 °C.

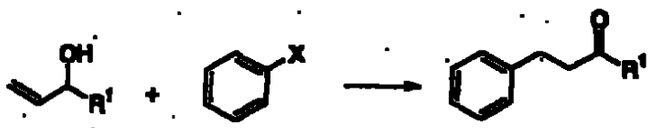


(28) (9)

The compounds of formula (9), wherein R^1, R^2, and R^{12} are as hereinbefore defined, and R^6 is hydrogen can be resolved or stereoisomerically enriched. Such compounds can be stereoisomerically enriched by allowing them to react with a chiral, non-racemic base to form a mixture of diastereomeric salts. Such diastereomeric salts can then be separated using techniques well-known to those of ordinary skill in the art, such as fractional crystallization. For example, a mixture of the diastereomeric salts can be dissolved in a suitable solvent and one diastereomeric salt may then crystallize from the solution after which time it may be collected, washed and dried. Suitable chiral, non-racemic bases include amine bases include, but are not limited to, one enantiomer of cis-1-amino-2-indanol, cinchonidine, 1-aminoindane, tert-leucinol, 2-amino-1,2-diphenylethanol, and alpha-methylbenzylamine. For example, a compound of formula (9), wherein R^1, R^2, and R^{12} are as hereinbefore defined, and R^6 is hydrogen, may be allowed to react with (1R,2S)-(+)-cis-1-amino-2-indanol in a suitable solvent, such as tetrahydrofuran to afford a mixture of diastereomeric salts. The solution containing the mixture of diastereomeric salts can then be allowed to slowly cool so that only one of the diastereomeric salts is appreciably soluble in the cooled solvent. The remaining diastereomeric salt may then precipitate out of the solution in the form of a crystalline solid comprising one diastereomeric salt in substantially pure form. The desired stereoisomerically enriched compound of formula (9) may then be obtained from either the precipitated diastereomeric salt or from the diastereomeric salt that remained in solution. The compound of formula (9), wherein R^6 is hydrogen, may then be obtained from the substantially pure diastereomeric salt by reaction with a suitable acidic compound, such as citric acid.

Compounds of formula (14), wherein R^6 is hydrogen, C_1-C_6 alkyl, -Si(C_1-C_6 alkyl)$_3$, or -CH_2(C_6-C_{10} aryl), wherein said C_6-C_{10} aryl group is optionally substituted with at least one substituent selected from halogen,C_1-C_6 alkyl, -OH, -OCH_3, and –N(C_1-C_6 alkyl)$_2$, are either commercially available or can be prepared according to methods known to those of ordinary skill in the art.

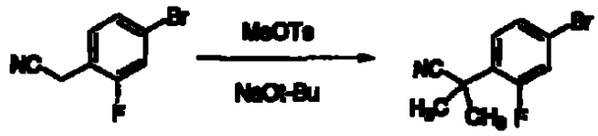
Compounds of formula (26) can be prepared via a so-called Heck-type reaction. For example, the compound of formula (26), wherein R^1 is as hereinbefore defined and R^6 is $-(CH_2)_2Ph$, can be prepared from reaction of compounds of formula (27) with a compound of formula (28), wherein X is a group suitable for use in a palladium-catalyzed (Pd-catalyzed) Heck-type coupling reaction. Heck-type coupling reactions can be performed using a palladium based catalyst. Suitable catalysts include, but are not limited to, $Pd(OAc)_2$, $PdCl_2$, and $Pd(PPh_3)_4$. Furthermore, such reactions can be performed in the presence of a base, such as triethylamine, sodium acetate, lithium acetate, potassium acetate, sodium carbonate, potassium carbonate, or cesium carbonate. These reactions may be performed in a solvent that will not interfere with the desired chemical reaction. Furthermore, appropriate solvents include those that are known to those of skill in the art to be compatible with the reaction conditions and include alkyl esters and aryl esters, alkyl, heterocyclic, and aryl ethers, hydrocarbons, alkyl and aryl alcohols, alkyl and aryl halogenated compounds, alkyl or aryl nitriles, alkyl and aryl ketones, amides, and non-protic heterocyclic solvents. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, N-methylpyrrolidinone, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Next, these reactions can be performed at a temperature in the range from about 0 °C to about 150 °C, or in the range of from about 25 °C to about 150 °C, or in the range of from about 25 °C to about 100 °C, or in the range of from about 45 °C to about 100 °C, or in the range of from about 45 °C to about 75 °C. Last, in the compounds of formula (28), X is a group that is suitable for use in Heck-type reactions. Suitable groups include chloride, bromide, iodide, and triflate ($-OSO_2CF_3$).



(27) (28) (26)

Compounds of formula (28) are either commercially available or can be prepared by methods known to those of ordinary skill in the art. For example, 2-(4-bromo-2-fluorophenyl)-

2-methylpropanenitrile, compound (28a) can be prepared from (4-bromo-2-fluorophenyl)acetonitrile, compound (28b), by reaction with an alkylating agent, methyl tosylate for example, in the presence of a base, sodium t-butoxide for example, as shown below.

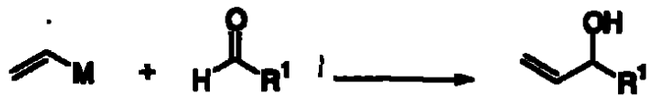


(28B) (28A)

Furthermore, (4-bromo-2-fluorophenyl)acetonitrile can be prepared from 4-bromo-1-(bromomethyl)-2-fluorobenzene by reaction with a cyanide salt, sodium cyanide for example, as shown below.



Compounds of formula (27), wherein R^1 is as hereinbefore defined, can be prepared by reaction of compounds of formula (29), wherein R^1 is as hereinbefore defined, and a compound of formula (30),



(30) (29) (27)

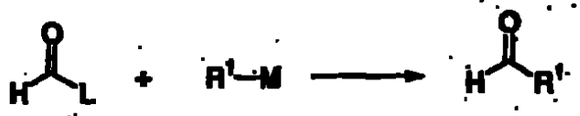
wherein M is a suitable metal, as shown. In the compounds of formula (30), M is chosen from a suitable metal, such as a magnesium derivative, such as magnesium bromide, or lithium. These reactions can be performed in an aprotic solvent, such as diethyl ether, methyl tert-butyl ether, or tetrahydrofuran for example. Additionally, these reactions can be performed at a temperature in the range of from about –78 °C to about 50 °C, or in the range of from about –78 °C to about 25 °C, or in the range of from about –78 °C to about 0 °C.

Compounds of formula (30), wherein M is a suitable metal group, are either commercially available or can be prepared by methods known to those of ordinary skill in the art. For example, the compound of formula (30) wherein M is –MgBr can be prepared from vinyl bromide and a suitable magnesium precursor, such as magnesium metal or activated Rieke magnesium. These reactions are can be performed in an aprotic solvent such as diethyl ether, methyl tert-butyl ether, or tetrahydrofuran, and at a temperature in the range of from about 0 °C to about 25 °C. Compounds of formula (30) wherein M is Li can be prepared

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from vinyl halides, such as vinyl bromide or iodide and a suitable alkyl lithium reagent, such as butyl lithium or tert-butyl lithium. These reactions can be performed in an aprotic solvent such as diethyl ether, methyl tert-butyl ether, or tetrahydrofuran, and at a temperature in the range of from about 0 °C to about 25 °C.

Compounds of formula (29), wherein R^1 is as hereinbefore defined, are either commercially available or can be prepared by reaction of a compound of formula (31), wherein L is a suitable leaving group, with a compound of formula (32), R^1 is as hereinbefore defined and M is a suitable metal. In the compounds of formula (31), L is a suitable leaving group, such a $-N(CH_3)_2$ group. In the compounds of formula (32), M is a suitable metal such as –MgBr or Li. These reactions are can be performed in an aprotic solvent such as diethyl ether, methyl tert-butyl ether, or tetrahydrofuran, and at a temperature in the range of from about 0 °C to about 25 °C.



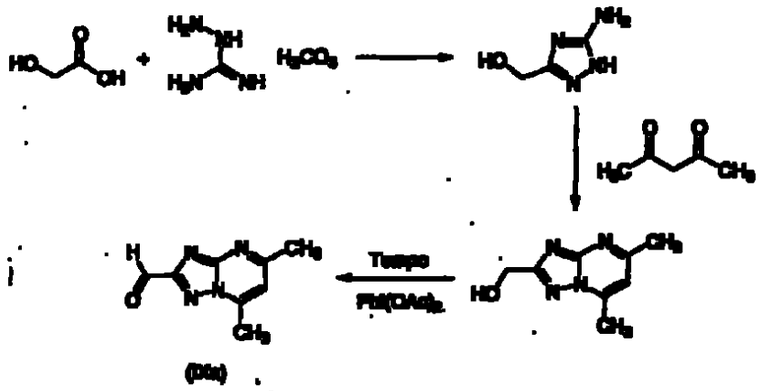
(31) (32) (29)

Compounds of formula (31) are either commercially available or can be prepared by methods known to those of ordinary skill in the art.

Compounds of formula (32) wherein M is a suitable metal are either commercially available or can be prepared by methods known to those of ordinary skill in the art. For example, the compound of formula (32) wherein M is –MgBr can be prepared from vinyl bromide and a suitable magnesium precursor, such as magnesium metal or activated Rieke magnesium. These reactions are can be performed in an aprotic solvent such as diethyl ether, methyl tert-butyl ether, or tetrahydrofuran, and at a temperature in the range of from about 0 °C to about 25 °C. Compounds of formula (32) wherein M is Li can be prepared from a suitable halide, such as a bromide or iodide and a suitable alkyl lithium reagent, such as butyl lithium or tert-butyl lithium. These reactions can be performed in an aprotic solvent such as diethyl ether, methyl tert-butyl ether, or tetrahydrofuran, and at a temperature in the range of from about 0 °C to about 25 °C.

Compounds of formula (24), such as (24a) below, are either commercially available or can be prepared using methods known to those of ordinary skill in the art. For example, the compound of formula (24a) was prepared by reaction of glycolic acid with aminoguanidine bicarbonate to afford (5-amino-1*H*-1,2,4-triazol-3-yl)methanol. The product was then allowed to react with 2,4-pentanedione to provide (5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-

yl)methanol, which was then oxidized using 2,2,6,6-tetramethyl-1-piperidinyloxy and iodobenzene diacetate to afford 5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde.



(IIa)

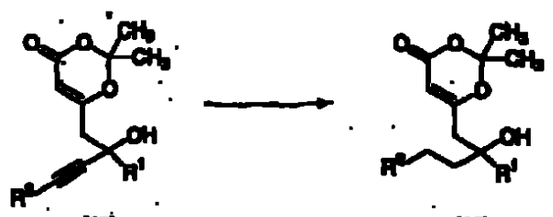
Compounds of formula (11), wherein R^1 is as hereinbefore defined and R^2 is an optionally substituted C_6-C_{10} aryl or an optionally substituted 4-10 membered heterocycle, can be prepared from compounds of formula (17) by reaction with a suitable base in a suitable solvent.



(17) (11)

Such reactions may be performed using a suitable base in a suitable solvent. Suitable bases include, but are not limited to, potassium carbonate, sodium carbonate, potassium bicarbonate, sodium bicarbonate, potassium hydroxide, and sodium hydroxide. Solvents that may be used include, but are not limited to, methyl alcohol, ethyl alcohol, iso-propyl alcohol, n-propyl alcohol, acetonitrile, and DMF, or a mixture of them. Additionally, water may be used as a cosolvent if necessary. These reactions may be performed at a temperature of from about 0 °C to about 150 °C. The particular choice of a base or combination of bases, solvent or combination of solvents, and reaction temperature will depend on the particular starting material being used and such choices are within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

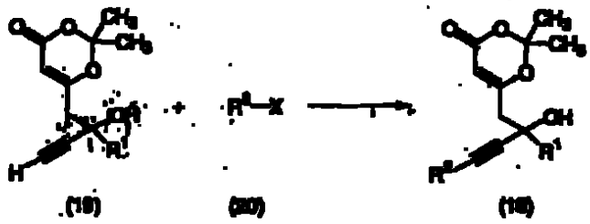
Compounds of formula (17), wherein R^1 is as hereinbefore defined and R^2 is an optionally substituted C_6-C_{10} aryl or an optionally substituted 4-10 membered heterocycle, can be prepared from compounds of formula (18) by reaction with a reducing agent in the presence of a catalyst.



(16) (17)

These reactions are typically performed in the presence of a metal catalyst, such as a palladium catalyst, a reducing agent, such as hydrogen, and in a solvent. Furthermore, these reactions may be performed at a temperature of from about 25 °C to about 150 °C, depending on the substrate, the catalyst, the reducing agent, and the solvent. Catalysts useful in such reactions include, but are not limited to, Pd on carbon (5% w/w and 10% w/w, for example), Pt on carbon (5% w/w and 10% w/w, for example), palladium hydroxide, and Raney nickel. Suitable reducing agents that may be used include, but are not limited to, hydrogen and ammonium formate. When hydrogen is used as the reducing agent, it is advantageous to pressurize the reaction vessel with at least one atmosphere of hydrogen gas. Solvents that may be used include, but are not limited to, protic solvents, such as methyl and ethyl alcohol, and aprotic solvents such as acetonitrile, DMF, ethyl acetate, acetone, chloroform, and dichloromethane. The particular choice of a catalyst, reducing agent, solvent, and temperature will depend on the particular substrate being used and such choices are within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

Compounds of formula (18), wherein R^1 is as hereinbefore defined and R^6 is an optionally substituted C_6-C_{10} aryl or an optionally substituted 4-10 membered heterocycle, can be prepared from compounds of formula (19) by reaction with a compound of formula (20), wherein R^6 is an optionally substituted C_6-C_{10} aryl or an optionally substituted 4-10 membered heterocycle and X is a halogen (such as bromine or iodine) or $-OSO_2CF_3$, in the presence of a suitable catalyst.



(19) (20) (18)

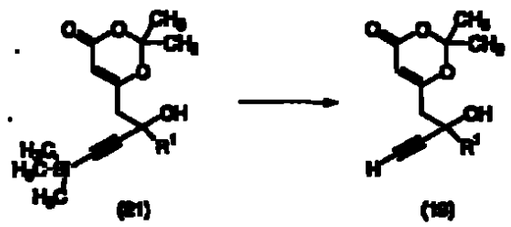
These reactions can be performed using a compound of formula (19), a compound of formula (20), a suitable catalyst, and a suitable copper compound (such as copper (I) iodide. These reactions are also performed in the presence of a base, such as diisopropyl amine, and in a solvent, such as dimethylformamide (DMF). These reactions may be performed at a

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temperature from 25 °C to 150 °C, depending on the particular substrates, the catalyst, and the solvents. Suitable catalysts include, but are not limited to, $PdCl_2(PPh_3)_2$, $PdCl_2$, and $Pd(PPh_3)_4$. Suitable bases include, but are not limited to, triethylamine, diethylamine, and diethylisopropyl amine. Solvents that may be used include, but are not limited to, acetonitrile, dimethylformamide (DMF), ethyl acetate, 1,2-dichloroethane, and chloroform. The particular choice of palladium catalyst, base, solvent, and temperature will depend on the particular substrates being used and such choices are within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

Compounds of formula (20), wherein R^9 is an optionally substituted C_6-C_{10} aryl or an optionally substituted 4-10 membered heterocycle, and X is a halogen (such as bromine or iodine) or $-OSO_2CF_3$, are either commercially available or can be prepared using methods known to those of ordinary skill in the art.

Compounds of formula (19), wherein R^1 is as hereinbefore defined, can be prepared from compounds of formula (21), wherein R^1 is as hereinbefore defined, with a suitable reagent or combination of reagents that will cleave the allyl group in compound (21).

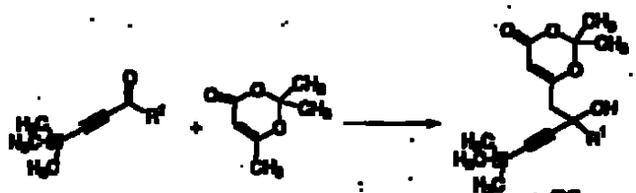


(21) (19)

Suitable reagents or combinations of reagents that will cleave the allyl group in the compound of formula (21) include, but are not limited to, strong bases, such as sodium hydroxide and potassium hydroxide, and fluoride ion (F^-). Suitable sources of fluoride ion include, but are not limited to, ammonium fluoride salts such as tetrabutyl ammonium fluoride. These reactions can be performed in a solvent or mixture of solvents that will not interfere with the desired chemical reaction. Suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent if it will not interfere with the desired

transformation. Finally, such reactions can be performed at a temperature in the range of from about 0 °C to about 100 °C, or in the range of from about 0 °C to about 75 °C, or in the range of from about 0 °C to about 50 °C, or in the range of from 25 °C to about 50 °C. The particular choice of a deprotecting reagent or combination of reagents, solvent, and temperature are within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

Compounds of formula (21), wherein R^1 is as hereinbefore defined, can be prepared from compounds of formula (22), wherein R^1 is as hereinbefore defined, by reaction with 2,2,6-trimethyl-[1,3]-dioxin-4-one.



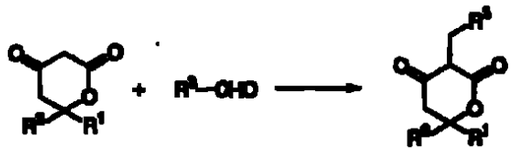
(22) (21)

These reactions can be performed in the presence of base that will deprotonate the 2,2,6-trimethyl-[1,3]-dioxin-4-one. Suitable bases include, but are not limited to, lithium diisopropyl amide, tert-butyl lithium, and n-butyl lithium. Bases such as lithium diisopropyl amide can be generated *in situ* by reaction with diisopropyl amine and an alkyl lithium reagent, such as tert-butyl lithium or n-butyl lithium, and can be used without isolation or further purification. These reactions can also be performed in a solvent that will not interfere with the desired chemical reaction. Suitable solvents include, but are not limited to, aprotic solvents such as diethyl ether, methyl tert-butyl ether, and tetrahydrofuran. Last, these reactions can be performed at a temperature in the range from about –78 °C to about ambient or room temperature, or in the range from about –78 °C to about 0 °C, or in the range from about –78 °C to about –30 °C. The choice of a particular base, solvent, and temperature are within the knowledge of one of ordinary skill in the art and such choices can be made without undue experimentation.

Compounds of formula (22), wherein R^1 is as hereinbefore defined, are either commercially available or can be prepared using methods known to those of ordinary skill the art, such as those found in *Journal of Organic Chemistry*, 1984, 4798-4800.

The compounds of formula (4) can be prepared in stereoisomerically enriched form by reaction of a compound of formula (11), which is stereoisomerically enriched with a compound of formula (12).

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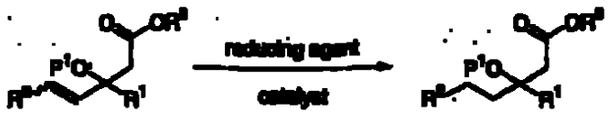


(11) (12) (4)

These reactions are generally performed in the presence of a reducing agent, such as a borane source or hydrogen in the presence of suitable catalyst. Suitable borane sources include, but are not limited to, borane-trimethylamine complex, borane-dimethylamine complex, borane t-butyl amine complex, and borane-pyridine complex. Suitable catalysts for use in the presence of a reducing agent such as hydrogen include, but are not limited to, nickel, palladium, rhodium and ruthenium. Furthermore, such reactions are performed in a solvent or mixture of solvents that will not interfere with desired chemical reaction. Furthermore, appropriate solvents include those that are known to those of skill in the art to be compatible with the reaction conditions and include alkyl esters and aryl esters, alkyl, heterocyclic, and aryl ethers, hydrocarbons, alkyl and aryl alcohols, alkyl and aryl halogenated compounds, alkyl or aryl nitriles, alkyl and aryl ketones, and non-protic heterocyclic solvents. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent if it will not interfere with the desired transformation. Finally, such reactions can be performed at a temperature in the range of from about 0 °C to about 75 °C, preferably in the range of from about 0 °C to about 32 °C, most preferably at room or ambient temperature. The choice of a particular reducing agent, solvent, and temperature will depend on several factors including, but not limited to, the identity of the particular reactants and the functional groups present in such reactants. Such choices are within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

Compounds of formula (9), wherein R^1, R^2, and R^3 are as hereinbefore defined, can be prepared from compounds of formula (8), wherein R^1, R^2, and R^3 are as hereinbefore defined, with a reducing agent in the presence of a catalyst.

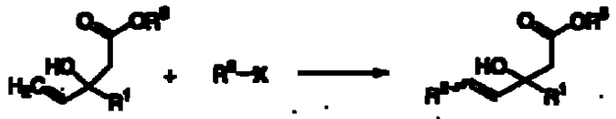
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(8) (9)

Suitable reducing agents for this reaction are those that are capable of transferring hydrogen (H_2) to the alkene to afford the desired alkane, compound (9). Suitable reducing agents include, but are not limited to hydrogen gas, formic acid, and formic acid salts, such as ammonium formate. When hydrogen gas is used as the reducing agent, the reaction vessel is usually pressurized with hydrogen gas. Suitable catalysts for this reaction include those that are capable of reducing the alkene in compound (8) to afford alkane (9) in the presence of the suitable reducing agents described above. Suitable catalysts include, but are not limited to, Pd (0), Pt (0), and Ni (0). These catalysts may be prepared *in situ* from suitable pre-catalysts that may be more shelf-stable. Suitable pre-catalysts include, but are not limited to, palladium on carbon (5 w/w% and 10 w/w%, for example), $PdCl_2$, $Pd(OH)_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $PtCl_2$, $Pt(OH)_2$, and Raney Nickel. Furthermore, these reactions can be performed in a solvent or mixture of solvents that will not interfere with the desired chemical reaction. Suitable solvents include, but are not limited to, alkyl esters and aryl esters; alkyl, heterocyclic, and aryl ethers, hydrocarbons, alkyl and aryl alcohols, alkyl and aryl halogenated compounds, alkyl or aryl nitriles, alkyl and aryl ketones, and non-protic heterocyclic solvents. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent if it will not interfere with the desired transformation. Finally, such reactions can be performed at a temperature in the range of from about 0 °C to about 100 °C, or in the range of from about 0 °C to about 75 °C, or in the range of from about 0 °C to about 50 °C, or in the range of from 25 °C to about 50 °C. The choice of a particular reducing agent, catalyst, solvent, and temperature will depend on a number of factors including, but not limited to, the identity of the reactants and the presence or absence of other functional groups. Such choices are within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

Compounds of formula (8), wherein R^1, R^2, and R^3 are as hereinbefore defined, can be prepared from compounds of formula (7), wherein R^1 and R^3 are as hereinbefore defined, by reaction with a compound of formula (6), wherein X is a halogen or $-OSO_2CF_3$, and R^2 is as hereinbefore defined, in the presence of a suitable catalyst.



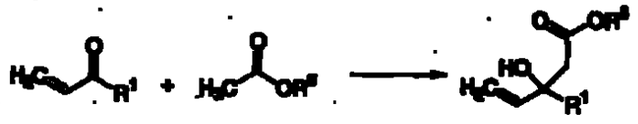
(7) (6) (8)

These reactions can be performed in the presence of a catalyst that is chemically and catalytically competent to perform a so-called Heck-type reaction. Suitable catalysts include Pd(0) species, either bound or unbound to an appropriate number of ligands. Such catalysts can be generated *in situ* from a suitable pre-catalyst in the presence of an appropriate ligand. Suitable pre-catalysts include, but are not limited to, $PdCl_2$, $PdCl_2(PPh_3)_2$, and $Pd(PPh_3)_4$. The amount of catalyst or pre-catalyst used in these reactions will depend on the particular reaction substrates, the temperature at which the reaction is performed, and the solvent in which the reaction is performed. Catalyst loadings may be in the range of from about 0.01 mol% (based on the amount of either compound (7) or (6)) to about 99 mol%, or in the range of from about 0.01 mol% to about 50 mol%, or in the range of from about 0.01 mol% to about 25 mol%, or in the range of from about 0.01 mol% to about 10 mol%, or in the range of from about 0.01 mol% to about 5 mol%. These reactions can also be performed in the presence of a base. Suitable bases include, but are not limited to, organic bases, such as triethylamine and sodium acetate, and inorganic bases, such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, and cesium carbonate. These reactions can be performed in a solvent that will not interfere with the desired chemical reaction. Suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, 1-methyl-2-pyrrolidinone, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent if it will not interfere with the desired transformation. Finally, these reactions can be performed at a temperature in the range of from about 0 °C to about 150 °C, or in the range of from about 25 °C to about 150 °C, or in the

range of from about 25 °C to about 100 °C. The particular choice of a catalyst, base, solvent, and temperature are all within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

Compounds of formula (6), wherein X is a halogen or $-OSO_2CF_3$, and R^6 is as hereinbefore defined are either commercially available or can be prepared according to methods known to those of ordinary skill in the art.

Compounds of formula (7), wherein R^1 and R^6 are as hereinbefore defined, can be prepared from compounds of formula (13), wherein R^1 is as hereinbefore defined, by reaction with a compound of formula (14), wherein R^6 is C_1-C_6 alkyl.



(13) (14) (7)

These reactions can be performed in the presence of a suitably basic compound that is capable of deprotonating the compound of formula (14). Suitable bases include, but are not limited to, lithium hexamethyldisilazide (LiHMDS), and lithium diisopropyl amide (LDA). Furthermore, these reactions can be performed in the presence of a solvent that will not interfere with the desired chemical reaction. Suitable solvents include, but are not limited to, dimethoxyethane, diisopropyl ether, chlorobenzene, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Last, these reactions can be performed at a temperature in the range of from about –78 °C to about 25 °C, or in the range of from about –78 °C to about 0 °C. The particular choice of a base, solvent, and temperature are within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

Compounds of formula (7), wherein R^1 is as hereinbefore defined and R^6 is hydrogen, can be prepared in stereoisomerically enriched form from a racemic or scalemic compound of formula (7), wherein R^1 is as hereinbefore defined and R^6 is hydrogen, by: a) reaction with a chiral, non-racemic base to afford a mixture of diastereomeric salts; b) separation of the diastereomeric salts from each other; and 3) conversion to the compound of formula (7) by reaction with a suitable acidic compound. Suitable chiral, non-racemic bases include chiral, non-racemic amines. Useful chiral, non-racemic amines include, but are not limited to, (S)-1,2,3,4-tetrahydro-1-napthylamine, (R)-1,2,3,4-tetrahydro-1-napthylamine, (S)-(-)-1-(2-napthyl)ethylamine, (R)-(-)-1-(2-napthyl)ethylamine, (1R,2S)-(-)-norephedrine,

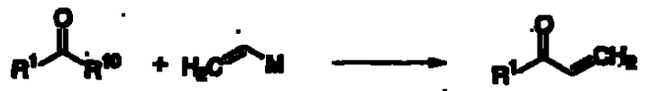
(1S,2R)-(-)-norephedrine. These reactions can be performed in a solvent that will not interfere with the desired chemical reaction. Suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent if it will not interfere with the desired transformation. Finally, these reactions can be performed at a temperature in the range of from about 0 °C to about 150 °C, or in the range of from about 25 °C to about 150 °C, or in the range of from about 25 °C to about 100 °C, or at ambient temperature. The solvent can be chosen such that one of the diastereomeric salts is appreciably soluble in the solvent while the other diastereomeric salt is appreciably insoluble in the solvent. Such a difference in solubilities can be used to affect separation of the diastereomeric salts from each other by the precipitation of one of the diastereomeric salts in stereoisomerically enriched form. After precipitation of substantially one diastereomeric salt, the stereoisomeric purity of the salt can be further increased by repeated recrystallization from an appropriate solvent or mixture of solvents. Conversion of a stereoisomerically enriched diastereomeric salt can be performed by reaction of the salt with a suitable acidic compound. Suitable acids include, but are not limited to inorganic acids (such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid) and organic acids (such as acetic acid, formic acid, and citric acid).

Alternatively, the compound of formula 7, wherein R^1 is as hereinbefore defined and R^2 is hydrogen, can be obtained in stereoisomerically enriched form by reaction with a chiral, non-racemic alcohol, to afford a mixture of diastereomeric esters. The diastereomeric esters can be obtained by reaction of the compound of formula (7) with the desired alcohol in the presence of a suitable activating agent or mixture of activating agents. Suitable activating agents include, but are not limited to, carbodiimides (such as diethylcarbodiimide), diethylazodicarboxylate, thionyl chloride, phosgene, and triphosgene. Reaction of the desired chiral, non-racemic alcohol with the activated compound of formula (7) can be performed in the presence of a suitable base. Suitable bases include, but are not limited to, organic bases such as triethylamine, diethylisopropylamine, pyridine, and 4,4-N,N-dimethylaminopyridine. Once obtained, the diastereomeric ester compounds of formula (7)

can be separated from each other using methods known to those of ordinary skill in the art, including, but not limited to, chromatography and fractional crystallization. The choice of a suitable chiral, non-racemic alcohol and conditions for the separation of the mixture of diastereomeric esters are within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

Compounds of formula (14) are either commercially available or can be prepared using methods known to those of ordinary skill in the art.

Compounds of formula (13), wherein R^1 is as hereinbefore defined, can be prepared from compounds of formula (15), wherein R^1 is as hereinbefore defined and R^{10} is a suitable leaving group, with a compound of formula (16), wherein M is a group capable of transferring the vinyl group of compound (16) to the compound of formula (15).



(15) (16) (13)

These reactions can be performed with a compound of formula (16), wherein M is a magnesium derivative, such as magnesium chloride or magnesium bromide, with a compound of formula (15), wherein R^{10} is a group $-N(OCH_3)CH_3$. These reactions can be performed in an aprotic solvent that will not interfere with desired chemical reaction. Suitable solvents include, but are not limited to, diethyl ether, tert-butyl methyl ether, diisopropyl ether, and tetrahydrofuran. Furthermore, such reactions can be performed at a temperature in the range of from about –78 °C to about 25 °C, or in the range of from about –78 °C to about 0 °C. The choice of a particular solvent and temperature are within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

Alternatively, compounds of formula (13) can be prepared by reaction of compounds of formula (15), wherein R^1 is as hereinbefore defined and R^{10} is a suitable leaving group, such as chloride, by reaction with a compound of formula (16), wherein M is a suitable group such as $-Si(CH_3)_3$. The compound of formula (15) wherein R^{10} is a suitable leaving group, such as chlorine, can be prepared from compounds of formula (15) wherein R^{10} is –OH by reaction with an activating agent. Suitable activating agents include, but are not limited to, oxalyl chloride, thionyl chloride, phosgene, and triphosgene. These reactions can be performed in a solvent that will not interfere with the desired chemical reaction. Suitable solvents include, but are not limited to, aprotic solvents such as dichloromethane, chloroform, 1,2-dichloroethane, and N,N-dimethylformamide (DMF). Reaction of the compound of formula (15) wherein R^{10} is a suitable leaving group, such as chlorine, with the compound of formula (16), wherein M is a suitable group such as $-Si(CH_3)_3$, can be performed in a solvent that will

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not interfere with the desired chemical reaction. Suitable solvents include, but are not limited to, aprotic solvents such as dichloromethane, chloroform, 1,2-dichloroethane, and N,N-dimethylformamide (DMF). Furthermore, such reactions can be performed in the presence of a Lewis acid to assist in the displacement of the leaving group by the vinyl group. Suitable Lewis acids include, but are not limited to, aluminum chloride, tin (IV) chloride, tin (II) chloride, and titanium tetrachloride. The amount of a particular Lewis acid required may vary from about 1 mol% to about 125 mol% (based on the vinyl silane reaction partner) and will depend on the identity of the Lewis acid used, the identity of the reaction partners, the solvent used, and the temperature at which the reaction is performed. Finally, these reactions can be performed at a temperature in the range from about –78°C to about 100 °C, or in the range of from about –78 °C to about 25 °C, or preferably in the range of from about –78°C to about 0 °C.

Compounds of formula (15) wherein R^{15} is a group $-N(OCH_3)CH_3$ can be prepared from compounds of formula (15) wherein R^{15} is a suitable leaving group, such as –Cl, by reaction N,O-dimethylhydroxylamine. These reactions are performed in the presence of a suitable base. Suitable bases include, but are not limited to, organic bases (such as triethylamine, pyridine, and N,N-4-dimethylaminopyridine) and inorganic bases (such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, and cesium carbonate). Furthermore, these reactions can be performed in a solvent that will not interfere with the desired chemical reaction. Suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent if it will not interfere with the desired transformation.

Compounds of formula (15) wherein R^{15} is –OH are commercially available or can be prepared by methods known to those of ordinary skill in the art.

Compounds of formula (16) wherein M is a magnesium derivative, such as –MgBr or –MgCl, are either commercially available or can be prepared from compounds of formula (16) wherein M is a halogen, preferably bromine or iodine, by reaction with a suitable magnesium reagent. Suitable magnesium reagents include, but are not limited to, magnesium (0) and

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Rieke magnesium. These reagents are usually formed *in situ* in the reaction mixture and are used without isolation or further purification.

Compounds of formula (16) wherein M is $-Si(CH_3)_3$ are commercially available or can be prepared from compounds of formula (16) is a magnesium derivative, such as –MgBr or –MgCl by reaction with $XSi(CH_3)_3$, wherein X is chlorine, bromine, or iodine. These compounds are usually formed *in situ* in the reaction mixture and are used without further purification or isolation.

The following Examples are meant to illustrate particular embodiments of the present invention only and are not intended to limit its scope in any manner.

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about". Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

Examples

In the examples described below, unless otherwise indicated, all temperatures in the following description are in degrees Celsius (°C) and all parts and percentages are by weight, unless indicated otherwise.

Various starting materials and other reagents were purchased from commercial suppliers, such as Aldrich Chemical Company or Lancaster Synthesis Ltd., and used without further purification, unless otherwise indicated.

The reactions set forth below were performed under a positive pressure of nitrogen, argon or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents. Analytical thin-layer chromatography was performed on glass-backed silica gel 60°F 254 plates (Analtech (0.25 mm)) and eluted with the appropriate solvent ratios (v/v). The reactions were assayed by high-pressure liquid chromatography (HPLC) or thin-layer chromatography (TLC) and terminated as judged by the consumption of starting material. The TLC plates were visualized by UV, phosphomolybdic acid stain, or iodine stain.

^{1}H-NMR spectra were recorded on a Bruker instrument operating at 300 MHz or 400 MHz and ^{13}C-NMR spectra were recorded at 75 MHz. NMR spectra are obtained as DMSO-d_6 or $CDCl_3$ solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm

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and 77.00 ppm) or DMSO-d_6 (2.50 ppm and 39.52 ppm). Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened, dd = doublet of doublets, dt = doublet of triplets. Coupling constants, when given, are reported in Hertz.

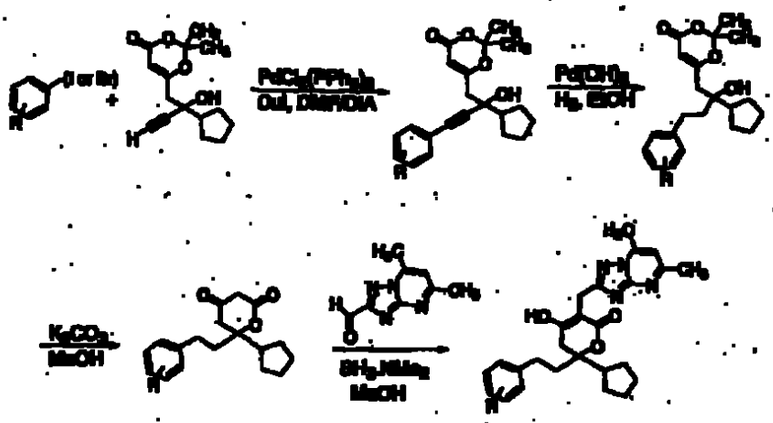
Infrared spectra were recorded on a Perkin-Elmer FT-IR Spectrometer as neat oils, as KBr pellets, or as $CDCl_3$ solutions, and when reported are in wave numbers (cm^{-1}). The mass spectra were obtained using LC/MS or APCI. All melting points are uncorrected.

All final products had greater than 95% purity (by HPLC at wavelengths of 220nm and 254nm).

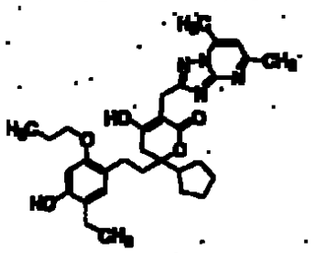
In the following examples and preparations, "Et" means ethyl, "Ac" means acetyl, "Me" means methyl, "Ph" means phenyl, "$(PhO)_2POCl$" means chlorodiphenylphosphate, "HCl" means hydrochloric acid, "EtOAc" means ethyl acetate, "Na_2CO_3" means sodium carbonate, "NaOH" means sodium hydroxide, "NaCl" means sodium chloride, "NEt_3" means triethylamine, "THF" means tetrahydrofuran, "DIC" means diisopropylcarbodiimide, "HOBt" means hydroxy benzotriazole, "H_2O" means water, "$NaHCO_3$" means sodium hydrogen carbonate, "K_2CO_3" means potassium carbonate, "MeOH" means methanol, "i-PrOAc" means isopropyl acetate, "$MgSO_4$" means magnesium sulfate, "DMSO" means dimethylsulfoxide, "AcCl" means acetyl chloride, "CH_2Cl_2" means methylene chloride, "MTBE" means methyl t-butyl ether, "DMF" means dimethyl formamide, "$SOCl_2$" means thionyl chloride, "H_3PO_4" means phosphoric acid, "CH_3SO_3H" means methanesulfonic acid, "Ac_2O" means acetic anhydride, "CH_3CN" means acetonitrile, "KOH" means potassium hydroxide, "CDI" means carbonyl diimidazole, "DABCO" means 1,4-diazabicyclo[2.2.2]octane, "IPE" means isopropyl ether, "MTBE" means methyl tert-butyl ether, "Et_2O" means diethylether, "Na_2SO_4" means sodium sulfate, "NBS" means N-bromosuccinimide, "TEA" means triethylamine, "DCM" means dichloromethane, "TBAB" means tetrabutylammonium bromide, "HMPA" means hexamethylphosphoramide, "NMP" means 1-methyl-2-pyrrolidinone, "DMAC" means N,N-dimethylacetamide, "h" means hours, "min" means minutes, "mol" means moles, and "rt" means room temperature.

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Scheme 1: Sonogashira Route

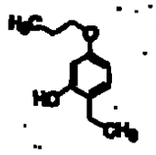


Example A(1): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethyl-4-hydroxy-2-propoxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



5,7-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde (0.24 g, 1.4 mmol, from step 8 below) was added to a solution of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione (0.45g, 1.2 mmol, from step 5 below) in MeOH (15 mL). The reaction mixture was stirred for 15 mins and then treated with borane-dimethylamine complex (100 mg, 1.7 mmol). After 15 hours the reaction mixture was filtered through a glass frit washing with MeOH. The filtrate was concentrated to a yellow oil. Purification by prep HPLC gave the product as a white powder (230 mg, 36%). ^{1}H NMR (400MHz, DMSO-d_6): δ 0.84 (t, J=7.3 Hz, 3 H), 0.92 (t, J=7.6 Hz, 3 H), 1.32-1.89 (m, 10 H), 1.82 (m, 1 H), 1.98 (m, 1 H), 2.28-2.47 (m, 11 H), 2.49 (d, J=[illegible] Hz, 1 H), 2.67(d, J=17,5 Hz, 1 H), 3.61-3.73 (m, 4 H), 6.26 (s, 1 H), 6.63 (s, 1 H), 6.95 (s, 1 H), 6.97 (s, 1 H), 10.72 (s, 1 H). Anal. Calcd. For $C_{31}H_{42}N_4O_6$: C, 67.62; H, 7.25; N, 10.21. Found: C, 67.69; H, 7.40; N, 10.04.

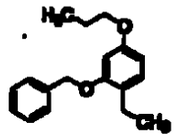
Step 1: 2-Ethyl-5-propoxy-phenol



Potassium carbonate (54 g, 0.39 mol) followed by 1-iodopropane (11.5 mL, 0.12 mol) were added to a solution of 2',4'-dihydroxyacetophenone (20 g, 0.13 mol) in DMF (150mL). The mixture was stirred for 5 hours and then partitioned between H_2O and EtOAc. The organic layer was washed with satd $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated to a clear oil (21.1g, 91%).

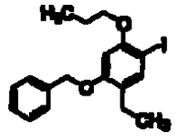
The oil was dissolved in MeOH (100 mL), treated with 10 wt % Pd/C (8g, Degussa type) and stirred under a balloon of H_2 for 24 hours. The reaction mixture was filtered through a pad of celite washing with EtOAc. The filtrate was concentrated and purified by flash column chromatography (0% to 20% EtOAc in hexanes) to give an orange oil (15g, 93%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, J=7.3 Hz, 3 H), 1.20 (t, J=7.6 Hz, 3 H), 1.78 (m, 2 H), 2.58 (q, J=7.6 Hz, 2 H), 3.86 (t, J=6.8 Hz, 2 H), 4.90 (s, 1H), 6.37 (d, J=2.5 Hz, 1 H), 6.44 (dd, J=8.1, 2.5 Hz, 1 H), 7.01 (d, J=8.3 Hz, 1 H).

Step 2: 2-Benzyloxy-1-ethyl-4-propoxy-benzene



Potassium carbonate (17.8 g, 0.13 mol) followed by benzyl bromide (5.12 mL, 42.9 mmol) were added to a solution of 2-ethyl-5-propoxy-phenol (7.74 g, 42.9 mmol) in DMF (60mL). The mixture was stirred at 45 °C for 15 hours and then partitioned between H_2O and EtOAc. The organic layer was washed with 1N HCl, brine, dried over Na_2SO_4 and concentrated to a brown oil. Purification by flash column chromatography (0% to 20% EtOAc in hexanes) gave the product as a clear oil (8.1g, 55%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.02 (t, J=7.6 Hz, 3 H), 1.19 (t, J=7.6 Hz, 3 H), 1.78 (q, J=7.6 Hz, 2 H), 2.63 (q, J=7.6 Hz, 2 H), 3.88 (t, J=6.6 Hz, 2 H), 5.05 (s, 2 H), 6.44 (dd, J=8.1, 2.3 Hz, 1 H), 6.51 (dd, J=2.3 Hz, 1 H), 7.05 (d, J=8.3 Hz, 1 H), 7.31 (m, 1 H), 7.36 (m, 2 H), 7.44 (m, 2 H).

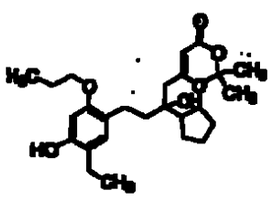
Step 3: 1-Benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene



A solution of iodine (2.82g, 11.1 mmol) dissolved in $CHCl_3$ (60 mL) was added dropwise to a stirred mixture of 2-benzyloxy-1-ethyl-4-propoxy-benzene (3g, 11.1 mmol), silver trifluoroacetate (2.45g, 11.1mmol) in $CHCl_3$ (20 mL). After the addition was complete the reaction mixture was stirred for 1 hour. The mixture was filtered through a pad of celite washing with CH_2Cl_2. The filtrate was washed with satd $Na_2S_2O_3$, brine, dried over Na_2SO_4 and concentrated to a pale

yellow solid (4.04g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (t, J=7.3 Hz, 3 H), 1.17 (t, J=7.6 Hz, 3 H), 1.81 (m, 2 H), 2.59 (q, J=7.6 Hz, 2 H), 3.90 (t, J=6.3 Hz, 2 H), 5.05 (s, 2 H), 6.43 (s, 1 H), 7.31-7.45 (m, 5 H), 7.49 9s, 1 H).

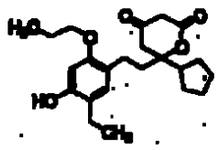
Step 4: 6-[2-Cyclopentyl-4-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-2-hydroxy-butyl]-2,2-dimethyl-[1,3]dioxin-4-one



A mixture of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene (4.0g, 10.1 mmol), 6-(2-cyclopentyl-2-hydroxybut-3-ynyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (2.42 g, 10.2 mmol, from step 11 below), $PdCl_2(PPh_3)_2$ (0.28 g, 4 mol%) and CuI (53 mg, 3 mol%). In diisopropylamine (12 mL) and DMF (12 mL) was heated at 90 °C for 90 min. The reaction mixture was cooled to room temperature and partitioned between 1N HCl and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to a black oil. Flash column chromatography (0% to 40% EtOAc in hexanes) gave a brown oil.

The oil was dissolved in EtOH (30 mL) and treated with $Pd(OH)_2$ (1g, 20wt%, Degussa type). The mixture was stirred under a balloon of hydrogen for 4 hours. The reaction mixture was filtered through a pad of celite washing with EtOAc. The filtrate was concentrated to an orange oil and purified by flash column chromatography to give the product as a yellow solid (0.83g, 16%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, J=7.3 Hz, 3 H), 1.20 (t, J=7.6 Hz, 3 H), 1.38-1.86 (br m, 19 H), 2.10 (m, 1 H), 2.44-2.55 (m, 6 H), 3.87 (t, J=6.8 Hz, 2 H), 4.60 (s, 1 H), 5.38 (s, 1 H), 6.35 (s, 1 H), 6.83 (s, 1 H).

Step 5: 6-Cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione

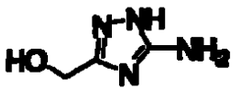


6-[2-Cyclopentyl-4-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-2-hydroxy-butyl]-2,2-dimethyl-[1,3]dioxin-4-one (0.8g, 1.8 mmol,) was dissolved in methanol (15 mL), treated with potassium carbonate (0.74g, 5.4 mmol) and heated at 45 °C under N_2 for 90 mins. The reaction mixture was partitioned between H_2O and IPE. The aqueous layer was made acidic with 1N HCl and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and

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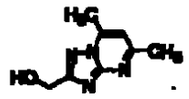
concentrated to give the product as a yellow foam (0.5 g, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (t, J=7.3 Hz, 3 H), 1.19 (t, J=7.6 Hz, 3 H), 1.41-1.87 (br m, 11 H), 1.95 (m, 1 H), 2.32 (m, 1 H), 2.49-2.80 (m, 6 H), 3.41 (m, 2 H), 3.85 (m, 2 H), 4.62 (s, 1 H), 6.39 (s, 1 H), 6.80 (s, 1 H).

Step 6: (5-Amino-1H-[1,2,4]triazol-3-yl)-methanol



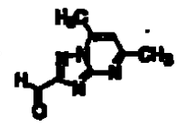
A solution of glycolic acid (70 % in water, 70 mL, 805 mmol) was added to aminoguanidine bicarbonate (55.12 g, 405 mmol) carefully. After foaming subsided, concentrated nitric acid (0.5 mL) was added and the entire reaction was refluxed for 40 hours. The reaction was cooled to 5 °C for 30 minutes, and the solids were filtered. The solids were then triturated with EtOH for 1 hour. The product was then filtered and dried under nitrogen (40.36 g, 82% yield). MS (ESI): 115 (M+H).

Step 7: (5,7-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-methanol



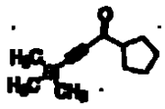
To a slurry of (5-amino-1H-[1,2,4]triazol-3-yl)-methanol (9.5 g, 50 mmol) from step 6 above in acetic acid (200 mL) was added 2,4-pentanedione (5.13 mL, 50 mmol). The mixture was heated to reflux for 4 hours, and then cooled to room temperature. The product was isolated by removing the solvent by rotary evaporation (8.5 g, 95% yield). MS (ESI): 179 (M+H).

Step 8: 5,7-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde



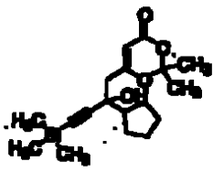
A slurry of 5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-methanol (0.3 g, 1.7 mmol) from step 7 above and IBX (1.4 g, 5.0 mmol) in 1,2-dichloroethane (22 mL) was stirred at 80 °C for 18 hours. The reaction was cooled to room temperature, and diluted with 100 mL CH_2Cl_2. After the solids were removed by filtration, the solvent was removed by rotary evaporation to give a yellow solid. The solid was purified by flash chromatography to give the desired product (229 mg, 77% yield). ^{1}H NMR ($CDCl_3$) δ: 2.72 (s, 3 H), 2.86 (s, 3 H), 6.96 (s, 1 H), 10.24 (s, 1 H).

Step 9: 1-Cyclopentyl-3-(trimethylsilyl)prop-2-yn-1-one



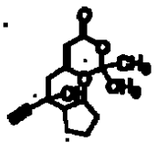
The title compound was prepared as described in the following reference: *Journal of Organic Chemistry* 1984, *106*, 4788-4800. ^{1}H NMR ($CDCl_3$) δ: 0.24 (s, 9 H), 1.69 (m, 4 H), 1.90 (m, 4 H), 2.92 (pentet, 1 H, *J*=7.5 Hz).

Step 10: 6-[2-Cyclopentyl-2-hydroxy-4-(trimethylsilyl)but-3-yn-1-yl]-2,2-dimethyl-4*H*-1,3-dioxin-4-one



A solution of diisopropylamine (3.85 mL, 27.5 mmol) dissolved in THF (100 mL) was cooled to -78 °C, where BuLi (11 mL, 27.5 mmol, 2.5 M in hexanes) was added dropwise over 10 minutes. After stirring at this temperature for 5 minutes the mixture was warmed to room temperature for 5 minutes, then cooled back to –78 °C, where 2,2,6-trimethyl-[1,3]dioxin-4-one (3.8 mL, 27.5 mmol) was added dropwise over the 5 minutes, then stirred an additional 30 minutes at -78 °C. To this solution was added 1-cyclopentyl-3-(trimethylsilyl)prop-2-yn-1-one (4.65 g, 25 mmol, from step 9) over 5 minutes. The resulting mixture was stirred at -78 °C for 1 hour, then slowly warmed to -30 °C and quenched with 0.5 N citric acid. The mixture was diluted with ether, washed with 1 N $NaHCO_3$, brine, dried with $MgSO_4$, and concentrated to give the crude product (9.4 g) contaminated with unreacted 2,2,6-trimethyl-[1,3]dioxin-4-one. ESIMS ($M+Na^+$): 369.1.

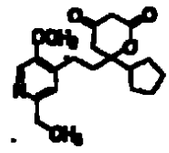
Step 11: 6-(2-Cyclopentyl-2-hydroxybut-3-ynyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one



A solution of crude 6-[2-cyclopentyl-2-hydroxy-4-(trimethylsilyl)but-3-yn-1-yl]-2,2-dimethyl-4*H*-1,3-dioxin-4-one (25 mmol), cesium fluoride (7.6 g, 50 mmol) dissolved in MeOH (75 mL) was stirred over night. The solvent was removed and the residue was diluted with EtOAc, washed with 0.5 N citric acid, 1 N $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. Purification by flash column chromatography (20% to 30% EtOAc in hexanes) gave the product (3.8 g, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.46-1.80 (m, 8 H), 1.72 (s, 3 H), 1.74 (s, 3 H), 2.13-2.18 (m, 1 H), 2.49 (s, 1 H), 2.58 (s, 1 H), 2.58 (s, 2 H), 5.43 (s, 1 H).

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121

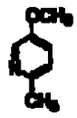
Example A(2): 6-Cyclopentyl-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]dihydro-2H-pyran-2,4(3H)-dione



6-[2-Cyclopentyl-4-(2-ethyl-5-methoxy-pyridin-4-yl)-2-hydroxy-but-3-ynyl]-2,2-dimethyl-[1,3]dioxin-4-one (1.8 g, 4 mmol, from step 6 below) was dissolved in EtOH (15 mL) and treated with $Pd(OH)_2$ (0.5g, 20wt% Degussa type). The mixture was stirred under a balloon of hydrogen for 2 hours. The reaction mixture was filtered through a pad of celite washing with EtOAc. The filtrate was concentrated to a pale yellow solid.

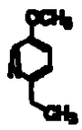
The solid was dissolved in methanol (10 mL), treated with potassium carbonate (1.28g, 9.3 mmol) and heated at 45 °C under N_2 for 60 mins. The reaction mixture was partitioned between H_2O and IPE. The aqueous layer was made neutral with 1N HCl and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give the product as a yellow solid (0.71 g, 51% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J=7.6 Hz, 3 H), 1.41-1.95 (br m, 8 H), 2.34 (m, 1 H), 2.65-2.76 (m, 6 H), 3.43 (m, 2 H), 3.88 (m, 5 H), 6.90 (s, 1 H), 8.09 (s, 1 H). Anal. Calcd. For $C_{22}H_{29}NO_4$: C, 69.64; H, 7.89; N, 4.05. Found: C, 69.23; H, 7.86; N, 3.99.

Step 1: 5-Methoxy-2-methyl-pyridine



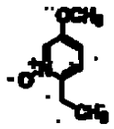
5-Hydroxy-2-methylpyridine (15g, 0.14 mol) was added to a stirred suspension of KOH (31g, 0.55 mol) in DMSO (150 mL). The mixture was stirred for 1 hour and then treated with methyl iodide (9.5 mL, 0.15 mol). After 20 mins the reaction mixture was poured into H_2O and extracted with ether. The ether extracts were dried over $MgSO_4$ and concentrated to a red oil. Purification by flash column chromatography (0% to 50% EtOAc in hexanes) gave the product as a clear oil (10.1g, 59%). ^1H NMR (400 MHz, $CDCl_3$): δ 2.49 (s, 3 H), 3.83 (s, 3 H), 7.08 (d, J=8.8 Hz, 1 H), 7.12 (d, J=8.3 Hz, 1 H), 8.19 (d, J=2.8 Hz, 1 H).

Step 2: 2-Ethyl-5-methoxy-pyridine



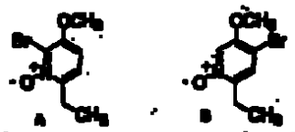
5-Methoxy-2-methyl-pyridine (9.5 g, 77 mmol) was added to a cooled -78 °C solution of LDA prepared from n-BuLi (37 mL, 93 mmol, 2.5 M in hexanes) and diisopropylamine (13 mL, 93 mmol) dissolved in THF (100 mL). The deep red reaction mixture was stirred for 30 mins and then treated with methyl iodide (5.4 mL, 85 mmol). After 2 hours the mixture was quenched with conc NH_4OH (15 mL). The mixture was poured into H_2O and extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to a red oil. Purification by flash column chromatography (0% to 40% EtOAc in hexanes) gave the product as a clear oil (2.5g, 24%) and unreacted starting material (3.8g, 40%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, J=7.3 Hz, 3 H), 2.76 (q, J=7.3 Hz, 2 H), 3.84 (s, 3 H), 7.08 (d, J=8.3 Hz, 1 H), 7.14 (d, J=8.3 Hz, 1 H), 8.23 (s, 1 H).

Step 3: 2-Ethyl-5-methoxy-pyridine 1-oxide



3-Chloroperoxybenzoic acid (5.68 g, 32.8 mmol) was added to a stirred solution of 2-ethyl-5-methoxy-pyridine (3 g, 22 mmol) dissolved in $CHCl_3$ (100 mL). The reaction was stirred at room temperature for 3 hours and then quenched with solid Na_2SO_3. The reaction mixture was partitioned between H_2O and CH_2Cl_2. The organic layer was washed with 1N NaOH, dried over Na_2SO_4 and concentrated to an oil (3.3g, 99%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J=7.5 Hz, 3 H), 2.89 (q, J=7.5 Hz, 2 H), 3.82 (s, 3 H), 6.86 (d, J=8.4 Hz, 1 H), 7.11 (d, J=8.3 Hz, 1 H), 8.04 (s, 1 H).

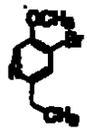
Step 4: 2-Bromo-6-ethyl-3-methoxy-pyridine 1-oxide (A) and 4-Bromo-2-ethyl-5-methoxy-pyridine 1-oxide (B)



Nitric acid (6 mL) was slowly added to a cooled 0 °C solution of 2-ethyl-5-methoxy-pyridine 1-oxide (3.4 g, 22.2 mmol) dissolved in sulfuric acid (6 mL). The mixture was heated to 90°C for 5 hours. The mixture was poured into ice, made basic with 15% NaOH and extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to a yellow oil. Purification by flash column chromatography (0% to 50% gave a mixture of nitro isomers as a yellow solid (1.58g, 38%)

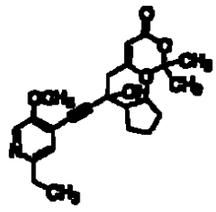
The solid was dissolved in acetic acid (30 mL) and treated with acetyl bromide (18 mL). The mixture was heated to 80 °C for 5 hours. The mixture was poured into ice, made basic with NaOH pellets and extracted with EtOAc. The organic layers were dried over Na_2SO_4 and concentrated to a yellow solid. Flash column chromatography (0% to 80% EtOAc in hexanes) gave 2-bromo-6-ethyl-3-methoxy-pyridine 1-oxide (0.82g, 18%). Further elution with 6% MeOH in CH_2Cl_2 gave 4-bromo-2-ethyl-5-methoxy-pyridine 1-oxide (1.31g, 74%). A: ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, J=7.3 Hz, 3 H), 2.95 (q, J=7.3 Hz, 2 H), 3.94 (s, 3 H), 6.79 (d, J=8.8 Hz, 1 H), 7.11 (d, J=8.8 Hz, 1 H). B: ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J=7.3 Hz, 3 H), 2.86 (q, J=7.3 Hz, 2 H), 3.90 (s, 3 H), 7.36 (s, 1 H), 7.98 (s, 1 H)

Step 5: 4-Bromo-2-ethyl-5-methoxy-pyridine



Phosphorous tribromide (5.5 mL) was added to a solution of 4-bromo-2-ethyl-5-methoxy-pyridine 1-oxide (1.25 g, 5.4 mmol) dissolved in CH_2Cl_2 (40 mL). The reaction mixture was heated to 50 °C for 1 hour. After cooling to room temperature the mixture was poured into ice and made basic with 15% NaOH and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated to a clear oil (1.13 g, 97%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, J=7.6 Hz, 3 H), 2.75 (q, J=7.6 Hz, 2 H), 3.97 (s, 3 H), 7.37 (s, 1 H), 8.13 (s, 1 H)

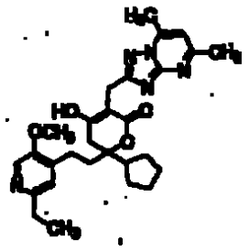
Step 6: 6-[2-Cyclopentyl-4-(2-ethyl-5-methoxy-pyridin-4-yl)-2-hydroxy-but-3-ynyl]-2,2-dimethyl-[1,3]dioxin-4-one



A mixture of 4-bromo-2-ethyl-5-methoxy-pyridine (1.1g, 5.1 mmol), 6-(2-cyclopentyl-2-hydroxybut-3-ynyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (1.22 g, 4.6 mmol), $PdCl_2(PPh_3)_2$ (0.13 g, 4 mol%) and CuI (27 mg, 3 mol%) in diisopropylamine (6 mL) and DMF (6 mL) was heated at 80 °C for 30 min. The reaction mixture was cooled to room temperature and partitioned between sat'd $NaHCO_3$ and EtOAc. The organic layer was washed with H_2O, brine, dried over Na_2SO_4 and concentrated to a brown oil. Flash column chromatography (0% to 80% EtOAc in hexanes) gave the product as a yellow oil (1.82, 89%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, J=7.6 Hz, 3

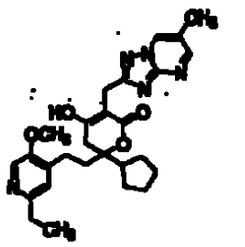
H), 1.60-1.84 (br m, 14 H), 2.26 (m, 1 H), 2.71 (m, 5 H), 3.91 (s, 3 H), 5.54 (s, 1 H), 7.05 (s, 1 H), 8.19 (s, 1 H).

Example A(3): 6-Cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-ethyl-5-methoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1) where 6-cyclopentyl-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]dihydro-2H-pyran-2,4(3H)-dione (example A(2)) was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione. ^{1}H NMR (400MHz, DMSO-d_6): δ 0.94 (t, J = 7.58 Hz, 3H), 1.19-1.58 (m, 6H), 1.83 (m, 1H), 1.91 (m, 1 H), 2.20 (m, 4 H), 2.29-2.37 (m, 6H), 2.43 (q, J = 7.58 Hz, 2H), 2.59 (d, J = 17.2 Hz, 1H), 3.50 (d, J = 16.2 Hz, 1H), 3.56 (s, 3 H), 3.61 (d, J = 16.2 Hz, 1H), 6.83 (s, 1 H), 6.85 (s, 1 H), 7.88 (s, 1 H), 10.82 (s, 1 H). Anal. Calcd. For $C_{32}H_{39}N_5O_4$•0.5 AcOH: C, 65.03; H, 6.96; N, 13.08. Found: C, 65.15; H, 7.05; N, 12.79.

Example A(4): 6-Cyclopentyl-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]-4-hydroxy-6-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one



6-Methyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde (0.13 g, 0.82 mmol, from step 2 below) was added to a solution of 6-cyclopentyl-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]dihydro-2H-pyran-2,4(3H)-dione (0.23g, 0.68 mmol, example A(2)) in MeOH (7 mL). The reaction mixture was stirred for 10 mins and then treated with borane-dimethylamine complex (60 mg, 0.68 mmol.). After 15 hours the reaction mixture was filtered through a glass frit washing with MeOH. The filtrate was concentrated to a yellow oil. Purification by prep HPLC gave the product as a white powder (58 mg, 17%). ^{1}H NMR (400MHz, DMSO-d_6): δ 1.22 (t, J = 7.6 Hz, 3H), 1.42-1.75 (m, 8H), 2.11 (m, 2 H), 2.41 (s, 3 H), 2.46-2.65 (m, 4 H), 2.70 (q, J = 7.6

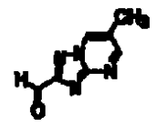
Hz, 2H), 2.83 (d, J = 17.7 Hz, 1H), 3.85 (m, 5 H), 7.13 (s, 1 H), 8.16(s, 1 H) 8.74 (s, 1 H), 8.93 (s, 1 H), 11.04 (s, 1 H). MS (ESI): 492.10 $(M+H)^+$.

Step 1: (6-Methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methanol



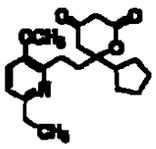
To a slurry of (5-amino-1H-[1,2,4]triazol-3-yl)-methanol (16.6 g, 87.8 mmol) from step 6 of example A(1) in acetic acid was added 3-ethoxymethacrolein (10 g, 87.8 mmol). The mixture was heated to 80 °C for 4 hours. Upon cooling of the reaction, the product crystallized out of solution. The collected product was awhite solid (14 g, 92%). ^{1}H NMR (300MHz, DMSO-d_6): δ 2.38 (s, 3 H), 4.63 (s, 2 H), 5.82 (s, 1 H), 8.75 (s, 1 H), 9.21 (s, 1 H).

Step 2: 6-Methyl[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde



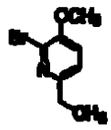
A slurry of (6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methanol (15.7 g, 95.8 mmol) from step 1 above, TEMPO (112mg, 7.2 mmol), Iodobenzene diacetate (33.9 g, 105.2 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 2 hours. Once the reaction was deemed complete, methyl tert-butyl ether (50 mL) was added slowly to precipitate the product. The concentrated mother liquor was introduced into a silica gel column and eluted with 2% MeOH/CH_2Cl_2 to give an additional amount of the aldehyde product as a white solid (12 g, 80%). ^{1}H NMR ($CDCl_3$) □: 2.54 (s, 3 H), 8.73 (s, 1 H), 8.85 (s, 1 H), 10.23 (s, 1 H).

Example A(8): 6-Cyclopentyl-5-[2-(5-ethyl-3-methoxypyridin-2-yl)ethyl]dihydro-2H-pyran-2,4(3H)-dione



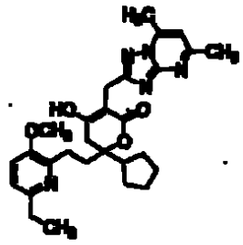
The title compound was prepared analogously to example A(2) where 2-bromo-6-ethyl-3-methoxy-pyridine from step 1 below was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, J=7.6 Hz, 3 H), 1.41-1.84 (br m, 8 H), 2.12 (m, 2 H), 2.37 (m, 1 H), 2.72 (m, 4 H), 2.89 (m, 2 H), 3.42 (m, 2 H), 3.79 (s, 3 H), 6.98 (d, J=8.3 Hz, 1 H), 7.08 (d, J=8.3 Hz, 1 H). MS (ESI): 346.10 $(M+H)^+$

Step 1: 2-Bromo-6-ethyl-3-methoxy-pyridine



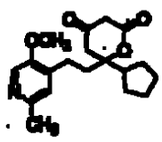
Phosphorous tribromide (1.3 mL) was added to a solution of 2-bromo-6-ethyl-3-methoxy-pyridine 1-oxide (0.3 g, 1.3 mmol, from step 4 of example A(2)) dissolved in CH_2Cl_2 (10 mL). The reaction mixture was heated to 50 °C for 1 hour. After cooling to room temperature the mixture was poured into ice and made basic with 15% NaOH and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated to a clear oil (0.28 g, 99%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, J=7.6 Hz, 3 H), 2.76 (d, J=7.6 Hz, 2 H), 3.89 (s, 3 H), 7.06 (d, J=8.1 Hz, 1 H), 7.09 (d, J=8.1 Hz, 1 H).

Example A(6): 6-Cyclopentyl-6-[(8,7-dimethyl[1,2,4]triazolo[1,5-a]pyridin-2-yl)methyl]-6-[2-(6-ethyl-3-methoxypyridin-2-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1) where 6-cyclopentyl-6-[2-(6-ethyl-3-methoxypyridin-2-yl)ethyl]dihydro-2H-pyran-2,4(3H)-dione (example A(5)) was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione. ^1H NMR (400MHz, DMSO-d_6): δ 1.15 (t, J = 7.58 Hz, 3H), 1.43-1.75 (m, 8H), 2.11 (s, 1 H), 2.22 (s, 1 H), 2.34-2.65 (m, 11 H), 2.74 (m, 2 H), 3.71 (s, 3 H), 3.73 (d, J = 16.4 Hz, 1H), 3.79 (d, J = 16.4 Hz, 1H), 7.02 (s, 1 H), 7.04 (d, J = 8.6 Hz, 1H), 8.59 (d, J = 8.6 Hz, 1H), 10.91 (s, 1 H). MS (ESI): 506.10 $(M+H)^+$

Example A(7): 6-Cyclopentyl-6-[2-(5-methoxy-2-methylpyridin-4-yl)ethyl]dihydro-2H-pyran-2,4(3H)-dione



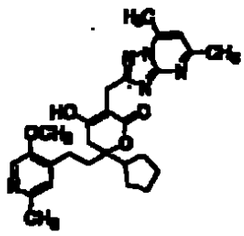
The title compound was prepared analogously to example A(2) where 5-methoxy-2-methyl-pyridine from step 1 of example A(2) was substituted in place of 2-ethyl-5-methoxy-pyridine in step 3 of that example. ^1H NMR (400 MHz, $CDCl_3$): δ 1.41-1.84 (br m, 8 H), 2.31

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(m, 1 H), 2.46 (s, 3 H), 2.57-2.76 (m, 4 H), 3.42 (s, 2 H), 3.86 (m, 5 H), 6.91 (s, 1 H), 8.04 (s, 1 H).

Anal. Calcd. For $C_{32}H_{39}NO_4$: C, 69.86; H, 7.80; N, 4.23. Found: C, 69.92; H, 7.75; N, 4.25.

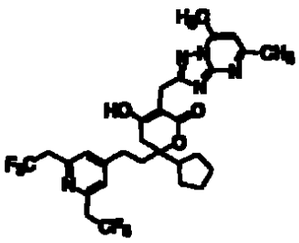
Example A(8): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-(5-methoxy-2-methylpyridin-4-yl)ethyl]-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1) where 6-cyclopentyl-6-[2-(5-methoxy-2-methylpyridin-4-yl)ethyl]dihydro-2H-pyran-2,4(3H)-dione (example A(7)) was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione. ^{1}H NMR (400MHz, DMSO-d_6): δ 1.45-1.78 (m, 8H), 2.11 (s, 1 H), 2.19 (s, 1 H), 2.41 (s, 3 H), 2.48 (m, 4 H), 2.55-2.62 (m, 6 H), 2.84 (d, J = 17.4 Hz, 1H), 3.76 (d, J = 16.0 Hz, 1H), 3.82 (s, 3 H), 3.89 (d, J = 16.0 Hz, 1H), 7.10 (s, 1 H), 7.12 (s, 1 H), 8.11 (s, 1 H), 11.15 (s, 1 H).

Anal. Calcd. For $C_{32}H_{39}N_3O_4$•0.5 AcOH: C, 64.47; H, 6.76; N, 13.43. Found: C, 64.42; H, 6.78; N, 13.39.

Example A(9): 6-[2-[2,6-Bis(2,2,2-trifluoroethyl)pyridin-4-yl]ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1) where 4-bromo-2,6-bis-(2,2,2-trifluoro-ethyl)-pyridine from step 5 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (400MHz, DMSO-d_6): δ 1.19-1.53 (m, 8H), 1.98 (m, 2H), 2.14-2.37 (m, 6H), 2.52 (m, 2H), 2.59 (d, J = 17.4 Hz, 1H), 3.50-3.67(m, 6 H), 6.86 (s, 1 H), 7.20 (s, 2 H), 10.79 (s, 1 H). MS (ESI): 612.15 $(M+H)^+$.

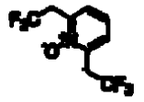
Step 1: 2,6-Bis-(2,2,2-trifluoro-ethyl)-pyridine

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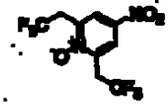
Trimethyl(trifluoromethyl)silane (11.8 mL, 75.5 mmol) was added to a stirred mixture of 2,6-bis(bromomethyl)pyridine (8g, 30.2 mmol), KF (4.4g, 75.5 mmol), CuI (17.3g, 90.8 mmol) in DMF (40 mL) and NMP (40 mL). The reaction mixture was heated to 85 °C under N_2 for 16 hours. The mixture was poured into water, made basic with 1N NaOH and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to a black oil. Flash column chromatography (0% to 30% EtOAc in hexanes) gave the product as a yellow oil (4.3g, 54%). ^1H NMR (400 MHz, $CDCl_3$): δ 3.91 (q, J=10.6 Hz, 4 H), 7.32 (d, J=7.6 Hz, 2 H), 7.71 (d, J=7.6 Hz, 1H).

Step 2: 2,6-Bis-(2,2,2-trifluoro-ethyl)-pyridine 1-oxide



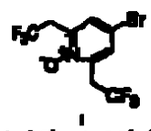
3-Chloroperoxybenzoic acid (4.62 g, 26.2 mmol) was added to a solution of 2,6-bis-(2,2,2-trifluoro-ethyl)-pyridine (4.25g, 17.5 mmol) in $CHCl_3$ (70 mL). The reaction was stirred at room temperature for 4 hours and then quenched with solid Na_2SO_3. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were washed with 1 N NaOH, brine, dried over Na_2SO_4 and concentrated to a yellow oil. Purification by flash column chromatography (0% to 50% EtOAc in hexanes) gave the product as a yellow solid (2.65g, 58%). ^1H NMR (400 MHz, $CDCl_3$): δ 3.98 (q, J=10.4 Hz, 4 H), 7.27 (t, J=8.1 Hz, 1 H), 7.47 (d, J=8.1 Hz, 2H).

Step 3: 4-Nitro-2,6-bis-(2,2,2-trifluoro-ethyl)-pyridine 1-oxide



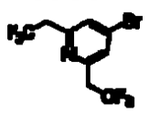
2,6-Bis-(2,2,2-trifluoro-ethyl)-pyridine 1-oxide (2.65 g, 10.22 mmol)was dissolved in H_2SO_4 (4mL) and cooled to 0°C. HNO_3 (8.2 mL) was added slowly and after the addition was complete the reaction mixture was heated to 90°C for 2 hours. The mixture was poured into ice, made basic with 15% NaOH and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to a red oil (2.72 g, 81%). ^1H NMR (400 MHz, $CDCl_3$): δ 3.95 (t, J=10.1 Hz, 4 H), 8.31 (s, 2 H).

Step 4: 4-Bromo-2,6-bis-(2,2,2-trifluoro-ethyl)-pyridine 1-oxide



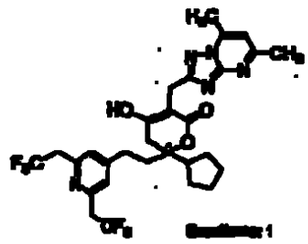
Acetyl bromide (14 mL) was added to a solution of 4-nitro-2,6-bis-(2,2,2-trifluoro-ethyl)-pyridine 1-oxide (2.7 g, 8.9 mmol) dissolved in AcOH (25 mL). The reaction mixture was heated to 80 °C for 5 hours. The reaction was cooled to room temperature, poured into ice, made basic with NaOH pellets and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to a red oil. Purification by flash column chromatography (0% to 30% EtOAc in hexanes) gave the product as a yellow oil (2.16 g, 72%). ^1H NMR (400 MHz, $CDCl_3$): δ 3.92 (t, J=10.1 Hz, 4 H), 7.59 (s, 2 H).

Step B: 4-Bromo-2,6-bis-(2,2,2-trifluoro-ethyl)-pyridine



A solution of 4-bromo-2,6-bis-(2,2,2-trifluoro-ethyl)-pyridine 1-oxide (2.1 g, 6.2 mmol) and PBr_3 (1 mL) in CH_2Cl_2 (15 mL) was stirred at room temperature for 4 hours. The reaction mixture was poured into ice, made basic with 15% NaOH and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to a pale yellow solid (1.77g, 89%). ^1H NMR (400 MHz, $CDCl_3$): δ 3.89 (t, J=10.4 Hz, 4 H), 7.51 (s, 2 H).

Example A(10): Enantiomer 1 of 6-[2-[2,6-Bis(2,2,2-trifluoroethyl)pyridin-4-yl]ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one

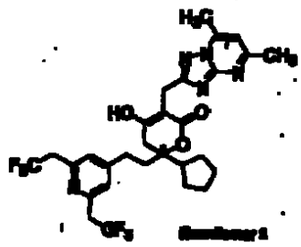


Enantiomer 1

The title compound was separated from racemic 6-[2-[2,6-Bis(2,2,2-trifluoroethyl)pyridin-4-yl]ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (65 mg, Example A(9)) using chiral HPLC (Chiralpak AS-H, 100 bar, 30% MeOH). (27 mg, 1.575 min retention time, 100% ee)

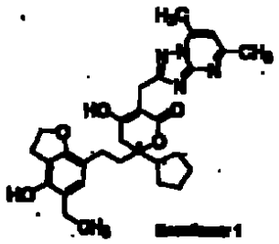
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Example A(11): Enantiomer 2 of 6-[2-[2,6-Bis(2,2,2-trifluoroethyl)pyridin-4-yl]ethyl]-6-cyclopentyl-3-[[5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]methyl]-4-hydroxy-5,6-dihydro-6H-pyran-2-one



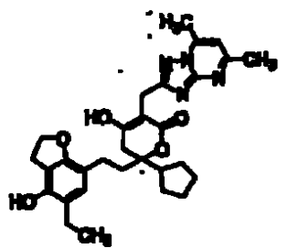
The title compound was separated from racemic 6-[2-[2,6-bis(2,2,2-trifluoroethyl)pyridin-4-yl]ethyl]-6-cyclopentyl-3-[[5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]methyl]-4-hydroxy-5,6-dihydro-6H-pyran-2-one (85 mg, Example A(9)) using chiral HPLC (Chiralpak AS-H, 100 bar, 30% MeOH). (29 mg, 3.203 min retention time, 100% ee)

Example A(12): Enantiomer 1 of 6-Cyclopentyl-3-[[5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]methyl]-6-[2-(5-ethyl-4-hydroxy-2,3-dihydro-1-benzofuran-7-yl)ethyl]-4-hydroxy-5,6-dihydro-6H-pyran-2-one



The title compound was separated from racemic 6-cyclopentyl-3-[[5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]methyl]-6-[2-(5-ethyl-4-hydroxy-2,3-dihydro-1-benzofuran-7-yl)ethyl]-4-hydroxy-5,6-dihydro-6H-pyran-2-one (280 mg, from step 1 below) using chiral HPLC (Chiralpak AS-H, 140 bar, 40% MeOH). (113 mg, 5.140 min retention time, 100% ee)

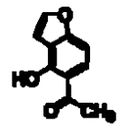
Step 1: 6-Cyclopentyl-6-[[5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]methyl]-6-[2-(5-ethyl-4-hydroxy-2,3-dihydro-1-benzofuran-7-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example X(x) where 1-(4-hydroxy-benzofuran-5-yl)-ethanone from step 1 below was substituted in place of 1-(4-ethoxy-3-hydroxy-phenyl)-ethanone in step 2 of that example.

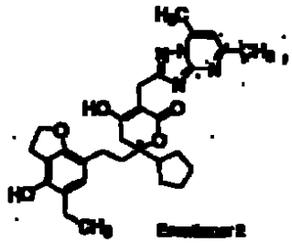
^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.08 (t, J=7.3 Hz, 3 H), 1.45-1.75 (br m, 8 H), 2.01 (m, 1 H), 2.15 (m, 1 H), 2.39-2.65 (m, 12 H), 2.80 (d, J=17.4 Hz, 1 H), 3.09 (t, J=8.8 Hz, 2 H), 3.77 (d, J=15.9 Hz, 1 H), 3.85 (d, J=15.9 Hz, 1 H), 4.47 (t, J= 11.4 Hz, 2 H), 6.64 (s, 1 H), 7.09 (s, 1 H), 8.58 (s, 1 H), 10.59 (s, 1 H). Anal. Calcd. For $C_{33}H_{38}N_4O_5$•0.4H_2O: C, 68.74; H, 6.57; N, 10.38. Found: C, 68.71; H, 6.85; N, 10.21.

Step 1: 1-(4-Hydroxy-benzofuran-5-yl)-ethanone



The title compound was prepared as described in the following reference: *Tetrahedron* 1995, *51*, 4909-4922. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 3 H), 7.00 (dd, J=2.0, 1.0 Hz, 1 H), 7.05 (dd, J=8.8, 1.0 Hz, 1 H), 7.57 (d, J=2.0 Hz, 1 H), 7.66 (d, J=8.8 Hz, 1 H), 13.3 (s, 1 H).

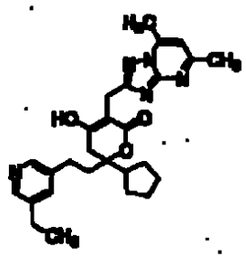
Example A(13): Enantiomer 2 of 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethyl-4-hydroxy-2,3-dihydro-1-benzofuran-7-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethyl-4-hydroxy-2,3-dihydro-1-benzofuran-7-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (280 mg, from step 1 of example

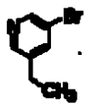
A(12)) using chiral HPLC (Chiralpak AS-H, 140 bar, 40% MeOH). (108 mg, 8.992 min retention time, 100% ee)

Example A(14): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethylpyridin-3-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



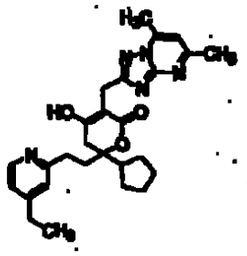
The title compound was prepared analogously to example A(1) where 3-bromo-5-ethyl-pyridine from step 1 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.14 (t, J=7.6 Hz, 3 H), 1.40-1.70 (br m, 8 H), 2.14 (m, 2 H), 2.44-2.65 (m, 12 H), 2.79 (d, J=17.6 Hz, 1 H), 3.72 (d, J=16.4 Hz, 1 H), 3.83 (d, J=16.4 Hz, 1 H), 7.04 (s, 1 H), 7.50 (s, 1 H), 8.24 (s, 1 H), 8.29 (s 1 H), 10.90 (s, 1 H). MS (ESI): 478.10 $(M+H)^+$

Step 1: 3-Bromo-5-ethyl-pyridine



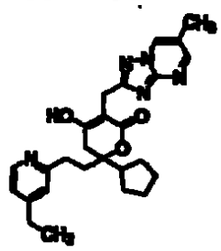
A mixture of NaOH (10 g, 0.25 mol), hydrazine monohydrate (10 mL) and 3-acetyl-5-bromopyridine (5g, 25 mmol) suspended in diethylene glycol (18 mL) was heated to 140 °C for 6 hours. The mixture was cooled to room temperature and partitioned between H_2O and ether. The ether extracts were dried over $MgSO_4$ and concentrated to a clear oil. Flash column chromatography (0% to 15% EtOAc in hexanes) gave the product as a clear oil (2.9 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, J=7.6 Hz, 3 H), 2.65 (d, J=7.6 Hz, 2 H), 7.57 (t, J=2.0 Hz, 1 H), 8.37 (d, J=1.8 Hz, 1 H), 8.51 (d, J=2.0 Hz, 1 H).

Example A(15): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(4-ethylpyridin-2-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



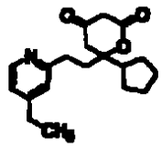
The title compound was prepared analogously to example A(1) where 2-bromo-4-ethyl-pyridine was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.99 (t, J=7.6 Hz, 3 H), 1.22-1.53 (br m, 8 H), 2.06 (m, 2 H), 2.24-2.44 (m, 10 H), 2.59 (m, 3 H), 3.56 (d, J=16.2 Hz, 1 H), 3.65 (d, J=16.2 Hz, 1 H), 6.87 (s, 1 H), 6.90 (d, J=5.0 Hz, 1 H), 6.97 (s, 1 H), 8.16 (d, J=5.0 Hz, 1 H), 10.77 (s, 1 H). Anal. Calcd. For $C_{29}H_{39}N_5O_3$•0.25 AcOH: C, 67.32; H, 6.99; N, 14.29. Found: C, 67.31; H, 7.02; N, 13.92.

Example A(16): 6-Cyclopentyl-6-[2-(4-ethylpyridin-2-yl)ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(4) where 6-cyclopentyl-6-[2-(4-ethyl-pyridin-2-yl)-ethyl]-dihydro-pyran-2,4-dione (from step 1 below) was substituted in place of 6-cyclopentyl-6-[2-(2-ethyl-5-methoxy-pyridin-4-yl)-ethyl]-dihydro-pyran-2,4-dione. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.07 (t, J=7.6 Hz, 3 H), 1.29-1.59 (br m, 8 H), 2.09 (m, 2 H), 2.25-2.52 (m, 6 H), 2.66 (m, 4 H), 3.64 (d, J=16.2 Hz, 1 H), 3.70 (d, J=15.9 Hz, 1 H), 6.97 (d, J=5.0 Hz, 1 H), 7.05 (s, 1 H), 8.24 (d, J=5.0 Hz, 1 H), 8.59 (s, 1 H), 8.66 (s, 1 H), 10.62 (s, 1 H). Anal. Calcd. For $C_{29}H_{31}N_5O_3$•0.3 AcOH: C, 66.62; H, 6.77; N, 14.60. Found: C, 66.63; H, 6.66; N, 14.24.

Step 1: 6-Cyclopentyl-6-[2-(4-ethyl-pyridin-2-yl)-ethyl]-dihydro-pyran-2,4-dione

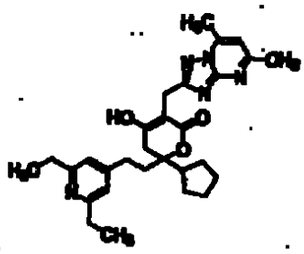


The title compound was prepared analogously to example A(2) where 2-bromo-4-ethyl-pyridine was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, J=7.6 Hz, 3 H), 1.41-1.82 (br m, 8 H), 2.14 (m, 2 H), 2.30 (m, 1 H), 2.63 (q, J=7.6 Hz, 2 H), 2.75 (m, 2 H), 2.86 (m, 2 H), 3.47 (m, 2 H), 7.01 (m, 2 H), 8.37 (s, 1 H). MS (ESI): 316.10 $(M+H)^+$

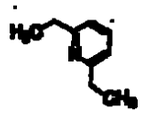
Example A(17): 6-Cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-3-[(5,7-diethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one

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The title compound was prepared analogously to example A(9) where 2,6-diethyl-pyridine from step 1 below was substituted in place of 2,6-bis-(2,2,2-trifluoro-ethyl)-pyridine in step 2 of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.16 (t, J=7.6 Hz, 6 H), 1.40-1.72 (br m, 8 H), 2.13 (m, 2 H), 2.41-2.67 (m, 14 H), 2.78 (d, J=17.1 Hz, 1 H), 3.70 (d, J=16.4 Hz, 1 H), 3.83 (d, J=16.4 Hz, 1 H),8.91 (s, 2 H), 7.05 (s, 1 H), 10.83 (s, 1 H). Anal. Calcd. For $C_{32}H_{39}N_5O_3$•0.5 AcOH: C, 67.52; H, 7.37; N, 13.12. Found: C, 67.70; H, 7.60; N, 12.91.

Step 1: 2,6-diethyl-pyridine

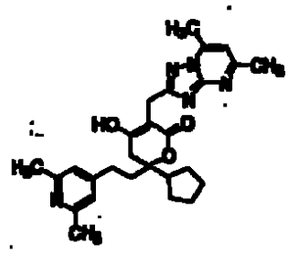


A mixture of NaOH (14.7 g, 0.37 mol), hydrazine monohydrate (15 mL) and 2,6-diacetylpyridine (6g, 36.8 mmol) suspended in diethylene glycol (27 mL) was cautiously heated to 120 °C for 16 hours. The mixture was cooled to room temperature and partitioned between H_2O and ether. The ether extracts were washed with 1 N NaOH, dried over $MgSO_4$ and concentrated to a clear oil. Flash column chromatography (0% to 15% EtOAc in hexanes) gave the product as a clear oil (2.9 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J=7.6 Hz, 3 H), 2.80 (d, J=7.6 Hz, 2 H), 6.97 (d, J=2.0 Hz, 2 H), 7.51 (t, J=7.6 Hz, 1 H).

2,6-Diethyl-pyridine has also been prepared as follows:

A solution of ethylmagnesium bromide in ethyl ether [prepared from Mg (16.5 g, 0.68 mol) and ethyl bromide (50 mL, 0.68 mol) in 500 mL of ether] was added dropwise to a mixture of 2,6-dichloropyridine (50 g, 0.34 mol) and $NiCl_2$(dppp) (1.0 g, 2 mol) in anhydrous ethyl ether (500 mL) at 0 °C under N_2 atmosphere. After addition, the resulting mixture was stirred at ambient temperature overnight, then heated to reflux for about 3 hours. The suspension was poured into crushed ice (200 g) and the mixture was saturated with NH_4Cl. The organic layer was separated and the aqueous phase was extracted with ether (200 mL x 3). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated to give the product (41.1g, 89%).

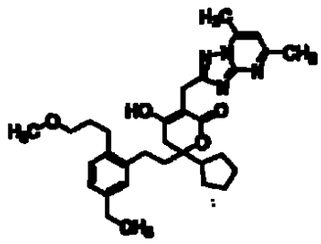
Example A(18): 6-Cyclopentyl-6-[2-(2,6-dimethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(9) where 2,6-lutidine N-oxide was substituted in place of 2,6-Bis-(2,2,2-trifluoro-ethyl)-pyridine 1-oxide in step 3 of that example.

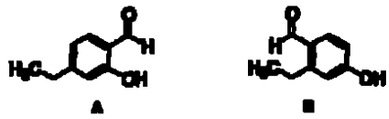
^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.44-1.75 (br m, 8 H), 2.19 (m, 2 H), 2.42-2.83 (m, 16 H), 2.85 (d, J=17.7 Hz, 1 H), 3.77 (d, J=16.1 Hz, 1 H), 3.89 (d, J=16.9 Hz, 1 H), 6.97 (s, 2 H), 7.12 (s, 1 H), 11.06 (s, 1 H). MS (ESI): 478.20 $(M+H)^+$

Example A(16): 6-Cyclopentyl-5-[[5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]methyl]-6-[2-[5-ethyl-2-(3-methoxypropyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1) where trifluoro-methanesulfonic acid 5-ethyl-2-(3-methoxy-propyl)-phenyl ester from step 5 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.06 (d, J=7.6 Hz, 3 H), 1.40-1.73 (br m, 10 H), 1.99 (s, 1 H), 2.18 (m, 1 H), 2.33 (s, 3 H), 2.40-2.57 (m, 11 H), 2.79 (d, J=17.4 Hz, 1 H), 3.16 (s, 3 H), 3.17 (d, J=7.6 Hz, 2 H), 3.70 (d, J=15.9 Hz, 1 H), 3.81 (d, J=15.9 Hz, 1 H), 6.94 (m, 3 H), 7.01 (s, 1 H), 10.95 (s, 1 H). MS (ESI): 548.72 $(M+H)^+$

Step 1: 4-Ethyl-2-hydroxy-benzaldehyde (A) and 2-Ethyl-4-hydroxy-benzaldehyde (B)



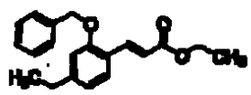
A B

Titanium(IV) chloride (100 mL, 100 mmol, 1M in CH_2Cl_2) followed by dichloromethyl methyl ether (7.47 mL, 82.5 mmol) was added to a cooled 0 °C solution of 3-ethylphenol (6.11g, 50 mmol). The reaction mixture was stirred for 45 mins. The mixture was poured into ice and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4

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and concentrated to a bright pink oil. Purification by flash column chromatography (0% to 10% EtOAc in hexanes) gave 4-ethyl-2-hydroxy-benzaldehyde (4.9g, 85%) followed by 2-ethyl-4-hydroxy-benzaldehyde (1.32 g, 18%). A: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, J=7.6 Hz, 3 H), 2.67 (d, J=7.6 Hz, 2 H), 6.82 (s, 1 H), 6.85 (d, J=8.0 Hz, 1 H), 7.48 (t, J=8.0 Hz, 1 H), 9.83 (s, 1 H), 11.05 (s, 1 H). B: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, J=7.6 Hz, 3 H), 3.08 (d, J=7.6 Hz, 2 H), 6.68 (s, 1 H), 6.78 (s, 1 H), 6.82 (d, J=8.3 Hz, 1 H), 7.77 (t, J=8.3 Hz, 1 H), 10.10 (s, 1 H).

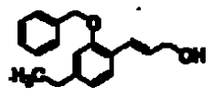
Step 2: 3-(2-Benzyloxy-4-ethyl-phenyl)-acrylic acid ethyl ester



Potassium carbonate (8.84 g, 64 mmol) followed by benzyl bromide (3.8 mL, 32 mmol) was added to a solution of 4-ethyl-2-hydroxy-benzaldehyde (4.8 g, 32 mmol) in DMF (60 mL). The mixture was stirred for 15 hours and then partitioned between 1N HCl and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to a brown oil. Purification by flash column chromatography (0% to 10% EtOAc in hexanes) gave the product as a yellow oil (8.1g, 84%).

The oil was dissolved in THF (40 mL) and treated with (carbethoxymethylene)triphenylphosphorane (3.5 g, 9.99 mmol). The reaction was heated at 70 °C for 5 days. The reaction mixture was concentrated and purified by flash column chromatography (0% to 15% EtOAc in hexanes) to give the product (2.93 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, J=7.6 Hz, 3 H), 1.32 (t, J=7.3 Hz, 3 H), 2.63 (d, J=7.6 Hz, 2 H), 4.24 (q, J=7.1 Hz, 2 H), 5.15 (s, 2 H), 6.49 (d, J=16.2 Hz, 1 H), 6.80 (m, 2 H), 7.39-7.47 (m, 6 H), 8.05 (d, J=16.2 Hz, 1 H).

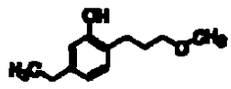
Step 3: 3-(2-Benzyloxy-4-ethyl-phenyl)-prop-2-en-1-ol



A solution of 3-(2-benzyloxy-4-ethyl-phenyl)-acrylic acid ethyl ester (2.9 g, 9.3 mmol) dissolved in ether (7 mL) was added to a cooled 0 °C suspension of lithium aluminium hydride (0.89 g, 23.4 mmol) in ether (20 mL). The reaction mixture was stirred for 4 hours, quenched with H_2O (3.6 mL) and 15% NaOH (0.9 mL) and then filtered through glass frit washing with ether. The filtrate was concentrated to a clear oil and purified by flash column chromatography (0% to 30% EtOAc in hexanes) to give the product (1.78 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, J=7.6 Hz, 3 H), 2.62 (q, J=7.6 Hz, 2 H), 4.29 (m, 2 H), 5.10 (s, 2 H), 6.35 (dt, J=16.2, 7.6 Hz, 1 H), 6.78 (s, 1 H), 6.80 (d, J=7.1 Hz, 1 H), 6.95 (d, J=16.2 Hz, 1 H), 7.32-7.45 (m, 6 H).

Step 4: 5-Ethyl-2-(3-methoxy-propyl)-phenol

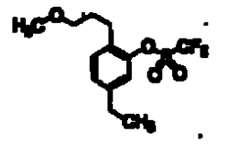
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Potassium hydroxide (1.17 g, 20.9 mmol) followed by methyl iodide (0.5 mL, 7.8 mmol) were added to a solution of 3-(2-benzyloxy-4-ethyl-phenyl)-prop-2-en-1-ol (1.4 g, 5.2 mmol) in DMSO (20 mL). The mixture was stirred for 15 hours and then partitioned between 1 N HCl and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to a brown oil. Purification by flash column chromatography (0% to 30% EtOAc in hexanes) gave a clear oil (1.0 g, 69%).

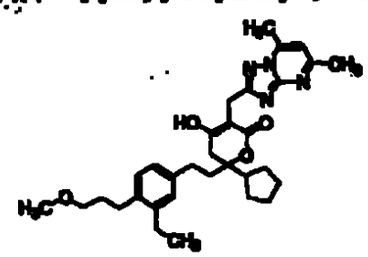
The oil was dissolved in EtOH (10 mL) and treated with $Pd(OH)_2$ (0.25g, 20wt%, Degussa type). The mixture was stirred under a balloon of hydrogen for 6 hours. The reaction mixture was filtered through a pad of celite washing with EtOAc. The filtrate was concentrated and purified by flash column chromatography to give the product (0.48g, 65%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, J=7.6 Hz, 3 H), 1.57 (m, 2 H), 2.58 (d, J=7.8 Hz, 2 H), 2.59 (d, J=6.6 Hz, 2 H), 3.37 (t, J=5.8 Hz, 2 H), 3.41 (s, 3 H), 6.70 (d, J=8.1 Hz, 1 H), 6.73 (s, 1 H), 6.88 (m, 2 H).

Step B: Trifluoro-methanesulfonic acid 5-ethyl-2-(3-methoxy-propyl)-phenyl ester



Trifluoromethanesulfonic anhydride (0.47 mL, 2.8 mmol) followed by triethylamine (0.42 mL, 3 mmol) was added to a cooled 0 °C solution of 5-ethyl-2-(3-methoxy-propyl)-phenol (0.45 g, 2.3 mmol). The reaction was stirred for 1 hour and then warmed to room temperature. The reaction was partitioned between 1 N HCl and EtOAc. The organic extracts were washed with brine, dried over Na2SO4 and concentrated to a black oil. ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, J=7.6 Hz, 3 H), 1.59 (m, 2 H), 2.65 (d, J=7.6 Hz, 2 H), 2.75 (t, J=7.6 Hz, 2 H), 3.35 (s, 3 H), 3.40 (t, J=7.6 Hz, 2 H), 7.07 (s, 1 H), 7.14 (d, J=8.0 Hz, 1 H), 7.23 (d, J=8.0 Hz, 1 H).

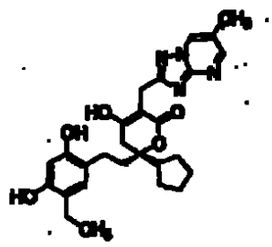
Example A(20): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)methyl]-6-(2-[3-ethyl-4-(3-methoxy-propyl)-phenyl]-ethyl)-4-hydroxy-5,6-dihydro-6H-pyran-2-one



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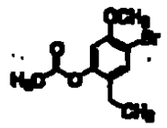
The title compound was prepared analogously to example A(19) where 2-ethyl-4-hydroxy-benzaldehyde from step 1 of example A(19) was substituted in place of 4-ethyl-2-hydroxy-benzaldehyde in step 2 of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.97 (t, J=7.6 Hz, 3 H), 1.29-1.60 (br m, 10 H), 1.98 (m, 2 H), 2.31-2.45 (m, 14 H), 2.66 (d, J=17.7 Hz, 1 H), 3.14 (s, 3 H), 3.23 (t, J=7.6 Hz, 2 H), 3.56 (d, J=16.9 Hz, 1 H), 3.71 (d, J=16.9 Hz, 1 H), 6.66 (m, 4 H), 10.06 (s, 1 H). MS (ESI): 547.20 $(M+H)^+$

Example A(21): (6R)-6-cyclopentyl-6-[2-(5-ethyl-2,4-dihydroxyphenyl)-ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one



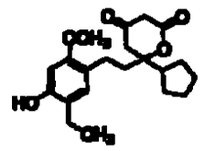
Boron tribromide (0.82 mL, 1M in CH_2Cl_2) was added to a cooled -78 °C of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-methoxy-phenyl)-ethyl]-4-hydroxy-3-(8-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-5,6-dihydro-pyran-2-one (70 mg, 0.14 mmol, from step 3 below) dissolved in CH_2Cl_2 (5 mL). The reaction was stirred for 16 hours. 1 N HCl was added and the reaction was stirred for 10mins. The mixture was extracted with 10% MeOH in EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to brown solid residue. Purification by prep HPLC gave the product as a brown solid (27 mg, 40%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.04 (t, J=7.3 Hz, 3 H), 1.40-1.75 (br m, 8 H), 1.98 (m, 2 H), 2.37-2.45 (m, 8 H), 2.57 (d, J=17.4 Hz, 1 H), 2.74 (d, J=17.4 Hz, 1 H), 3.78 (d, J=16.1 Hz, 1 H), 3.79 (d, J=16.1 Hz, 1 H), 6.33 (s, 1 H), 6.66 (s, 1 H), 6.69 (s, 1 H), 6.84 (m, 3 H), 10.90 (s, 1 H). MS (ESI): 492.55 $(M+H)^+$

Step 1: Acetic acid 4-bromo-2-ethyl-5-methoxy-phenyl ester



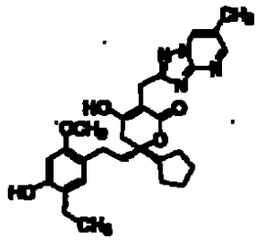
The title compound was prepared analogously to step 4 of example A(22) where methyl iodide was substituted in place of ethyl iodide in step 1 of that example. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, J=7.4 Hz, 3 H), 2.32 (s, 3 H), 2.45 (q, J=7.4 Hz, 2 H), 3.85 (s, 3 H), 6.59 (s, 1 H), 7.42 (s, 1 H).

Step 2: 6-Cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-methoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione



The title compound was prepared analogously to example A(2) where acetic acid 4-bromo-2-ethyl-5-methoxy-phenyl ester was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, J=7.4 Hz; 3 H), 1.41-1.86 (m, 9 H), 1.94 (m, 1 H), 2.34 (m, 1 H), 2.52 (m, 3 H), 2.62 (m, 1 H), 2.73 (d, J=16.4 Hz, 1 H), 2.76 (d, J=16.4 Hz, 1 H), 3.41 (s, 2 H), 3.75 (s, 3 H), 4.58 (s, 1 H), 6.35 (s, 1 H), 6.60 (s, 1 H).

Step 2: 6-Cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-methoxy-phenyl)-ethyl]-4-hydroxy-3-(6-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-5,6-dihydro-pyran-2-one

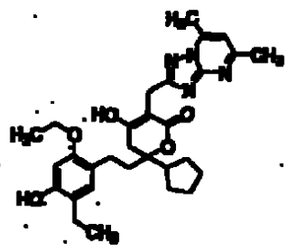


Racemic 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-methoxy-phenyl)-ethyl]-4-hydroxy-3-(6-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-5,6-dihydro-pyran-2-one was prepared analogously to example A(4) where 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-methoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione from step 2 above was substituted in place of 6-cyclopentyl-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]dihydro-2H-pyran-2,4(3H)-dione.

The title compound was separated from racemic 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-methoxy-phenyl)-ethyl]-4-hydroxy-3-(6-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-5,6-dihydro-pyran-2-one using chiral HPLC (Chiralpak AS-H, 140 bar, 40% MeOH). (5.85 min retention time). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.10 (t, J=7.6 Hz, 3 H), 1.44-1.76 (br m, 8 H), 2.04 (m, 2 H), 2.41-2.62 (m, 9 H), 2.61 (d, J=17.4 Hz, 1 H), 3.69 (s, 3 H), 3.79 (d, J=16.2 Hz, 1 H), 3.85 (d, J=16.2 Hz, 1 H), 6.44 (s, 1 H), 6.62 (s, 1 H), 6.74 (s, 1 H), 8.68 (s, 1 H), 9.10 (s, 1 H), 10.95 (s, 1 H).

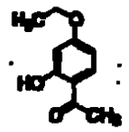
Example A(22): 6-Cyclopentyl-3-[(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-methyl]-6-[2-(2-ethoxy-5-ethyl-4-hydroxyphenyl)-ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one

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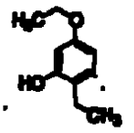
The title compound was prepared analogously to example A(1) where acetic acid 4-bromo-5-ethoxy-2-ethyl-phenyl ester from step 4 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.80 (t, J=7.3 Hz, 3 H), 1.03 (t, J=6.8 Hz, 3 H), 1.24-1.52 (br m, 8 H), 1.70 (m, 1 H), 1.85 (m, 1 H), 2.12-2.32 (m, 11 H), 2.37 (d, J=17.4 Hz, 1 H), 2.55 (d, J=17.4 Hz, 1 H), 3.51 (d, J=16.2 Hz, 1 H), 3.61 (m, 3 H), 6.13 (s, 1 H), 6.51 (s, 1 H), 6.83 (s, 1 H), 8.76 (s, 1 H), 10.61 (s, 1 H).
MS (ESI): 596.20 $(M+H)^+$

Step 1: 1-(4-Ethoxy-2-hydroxy-phenyl)-ethanone



Potassium carbonate (13.6 g, 99 mmol) followed by ethyl iodide (2.4 mL, 29.6 mmol) were added to a solution of 2',4'-dihydroxyacetophenone (5 g, 33 mmol) in DMF (50mL). The mixture was stirred for 4 hours and then partitioned between H_2O and EtOAc. The organic layer was washed with sat $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated to a clear oil. Purification by column chromatography gave the product as a white solid (3.7g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (t, J=6.8 Hz, 3 H), 2.55 (s, 3 H), 4.07 (d, J=7.1 Hz, 2 H), 6.40 (s, 1 H), 6.43 (d, J=8.8 Hz, 1 H), 7.62 (d, J=8.8 Hz, 1 H), 12.74 (s, 1 H).

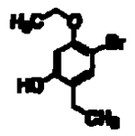
Step 2: 5-Ethoxy-2-ethyl-phenol



1-(4-Ethoxy-2-hydroxy-phenyl)-ethanone was dissolved in MeOH (40 mL), treated with 10 wt % Pd/C (1.4g, Degussa type) and stirred under a balloon of H_2 for 24 hours. The reaction mixture was filtered through a pad of celite washing with EtOAc. The filtrate was concentrated to give the product as an oil (3.12 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, J=7.6 Hz, 3 H), 1.39 (t, J=7.1 Hz, 3 H), 2.56 (d, J=7.6 Hz, 2 H), 3.96 (d, J=7.1 Hz, 2 H), 4.79 (s, 1 H), 6.37 (d, J=2.5 Hz, 1 H), 6.44 (dd, J=8.3, 2.5 Hz, 1 H), 7.01 (d, J=8.3 Hz, 1 H).

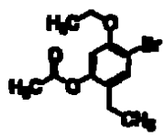
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Step 3: 4-Bromo-5-ethoxy-2-ethyl-phenol



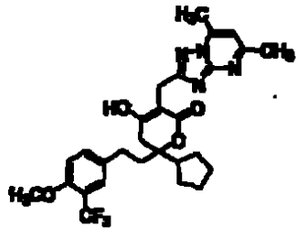
A solution of tetrabutyl ammonium tribromide (9.9 g, 20.5 mmol) in $CHCl_3$ (50 mL) was added to a stirred solution of 5-ethoxy-2-ethyl-phenol (3.1 g, 18.6 mmol) dissolved in $CHCl_3$ (50 mL). The reaction mixture was stirred for 30 mins and then quenched with 5% solution of sodium thiosulfate (30 mL). The biphasic mixture was stirred for 30 mins and then the layers were separated. The organic layer was washed with 1 N HCl, brine, dried over Na_2SO_4 and concentrated to a red oil. Purification by flash column chromatography (0% to 15% EtOAc in hexanes) gave the product as an oil (2.6 g, 59%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, J=7.6 Hz, 3 H), 1.44 (t, J=7.1 Hz, 3 H), 2.59 (q, J=7.6 Hz, 2 H), 4.06 (q, J=7.1 Hz, 2 H), 4.86 (s, 1 H), 6.41 (s,1 H), 7.25 (s, 1 H).

Step 4: Acetic acid 4-bromo-5-ethoxy-2-ethyl-phenyl ester



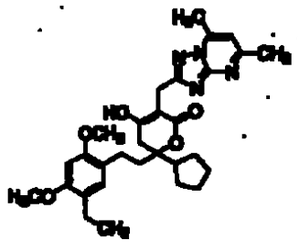
Acetyl chloride (0.91 mL, 12.8 mmol) followed by triethylamine (1.8 mL, 12.8 mmol) were added to a stirred solution of 4-bromo-5-ethoxy-2-ethyl-phenol (2.6 g, 10.7 mmol) dissolved in CH_2Cl_2 (20 mL). The reaction was stirred for 45 mins and then partitioned between 1N HCl and EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine dried over Na_2SO_4 and concentrated. Purification by flash column chromatography (0% to 20% EtOAc in hexanes) gave the product as a clear oil (1.64 g, 53%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, J=7.6 Hz, 3 H), 1.45 (t, J=7.1 Hz, 3 H), 2.31 (s, 3 H), 2.45 (q, J=7.6 Hz, 2 H), 4.05 (q, J=7.1 Hz, 2 H), 6.88 (s, 1 H), 7.41 (s, 1 H).

Example A(33): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[3-[4-methoxy-3-(trifluoromethyl)phenyl]ethyl]-5,6-dihydro-2H-pyran-2-one



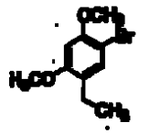
The title compound was prepared analogously to example A(1) where 4-bromo-2-(trifluoromethyl)anisole was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.19-1.51 (br m, 8 H), 1.93 (m, 2 H), 2.21-2.46 (m, 10 H), 2.60 (d, J=17.4 Hz, 1 H), 3.53 (d, J=16.2 Hz, 1 H), 3.64 (d, J=16.2 Hz, 1 H), 3.67 (s, 3 H), 6.87 (s, 1 H), 7.00 (d, J=8.8 Hz, 1 H), 7.22 (d, J=2.0 Hz, 1 H), 7.40 (d, J=17.4 Hz, 1 H), 10.76 (s, 1 H). MS (ESI): 545.10 $(M+H)^+$

Example A(24): 6-Cyclopentyl-3-[[5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]methyl]-6-[2-(5-ethyl-2,4-dimethoxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to Example A(1) where 1-bromo-5-ethyl-2,4-dimethoxy-benzene from step 1 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.82 (d, J=7.8 Hz, 3 H), 1.22-1.82 (br m, 8 H), 1.72 (m, 1 H), 1.88 (m, 1 H), 2.20-2.40 (m, 12 H), 2.58 (d, J=17.9 Hz, 1 H), 3.43 (s, 3 H), 3.52 (d, J=16.1 Hz, 1 H), 3.58 (s, 3 H), 3.81 (d, J=16.1 Hz, 1 H), 6.32 (s, 1 H), 6.83 (s, 1 H), 6.84 (s, 1 H), 10.70 (s, 1 H). MS (ESI): 535.20 $(M+H)^+$

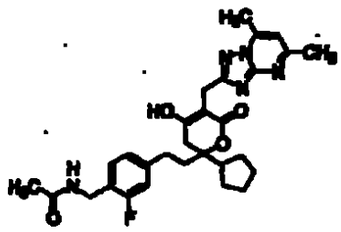
Step 1: 1-Bromo-5-ethyl-2,4-dimethoxy-benzene



A solution of tetrabutyl ammonium tribromide (15.4 g, 31.8 mmol) in $CHCl_3$ (100 mL) was added to a stirred solution of 4-ethyl resorcinol (4 g, 29 mmol) dissolved in $CHCl_3$ (50 mL). The reaction mixture was stirred for 2 hours and then quenched with 5% solution of sodium thiosulfate (50 mL). The biphasic mixture was stirred for 30 mins and then the layers were separated. The organic layer was washed with 1 N HCl, brine, dried over Na_2SO_4 and concentrated to yellow oil. The oil was dissolved in DMF (60 mL) and treated with K_2CO_3 (12.7 g, 92 mmol), followed by methyl iodie (2.9 mL, 46 mmol). The mixture was stirred for 15 hours and then partitioned between H_2O and EtOAc. The organic layers were washed with 1 N HCl, brine, dried over Na_2SO_4 and concentrated to a dark red oil. Purification by flash column chromatography (0% to 10% EtOAc in hexanes) gave the product as a yellow oil (2.8 g, 39%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, J=7.6 Hz, 3 H), 2.54 (q, J=7.6 Hz, 2 H), 3.83 (s, 3 H), 3.89 (s, 3 H), 6.46 (s, 1 H), 7.26 (s, 1 H).

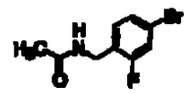
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Example A(29): N-[4-(2-(6-Cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-2-oxo-3,6-dihydro-2H-pyran-5-yl)ethyl)-3-fluorobenzyl]acetamide



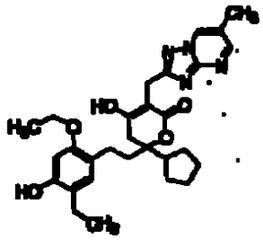
The title compound was prepared analogously to example A(1) where 4-bromo-2-(trifluoromethyl)anisole was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.38-1.69 (br m, 8 H), 1.88 (s, 3 H), 2.12 (m, 2 H), 2.39-2.63 (m, 10 H), 2.77 (d, *J*=17.2 Hz, 1 H), 3.71 (d, *J*=16.2 Hz, 1 H), 3.83 (d, *J*=16.2 Hz, 1 H), 4.23 (d, *J*=5.8 Hz, 2 H), 7.04 (m, 3 H), 7.21 (t, *J*=7.8 Hz, 1 H), 8.29 (t, *J*=5.8 Hz, 1 H), 10.99 (s, 1 H). MS *(ESI)*: 536.20 $(M+H)^+$

Step 1: N-(4-Bromo-2-fluoro-benzyl)-acetamide



Acetyl chloride (0.7 mL, 9.9 mmol) followed by triethylamine (2.8 mL, 19.9 mmol) were added to a suspension of 4-bromo-2-fluorobenzylamine hydrochloride (2g, 8.3 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 90 mins and then partitioned between 1 N HCl and EtOAc. The organic layers were brine, dried over Na_2SO_4 and concentrated. Purification by flash column chromatography (0% to 60% EtOAc in hexanes) gave the product as a clear oil (1.5 g, 74%). MS (ESI): 246.10, 248.10 $(M+H)^+$

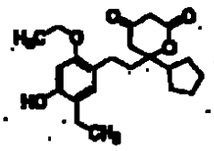
Example A(30): 6-Cyclopentyl-6-[2-(2-ethoxy-5-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-3-[(3-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(4) where 6-cyclopentyl-6-[2-(2-ethoxy-5-ethyl-4-hydroxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione from step 1 below was substituted in place of 6-cyclopentyl-6-[2-(2-ethyl-5-methoxy-pyridin-4-yl)-ethyl]-dihydro-pyran-2,4-

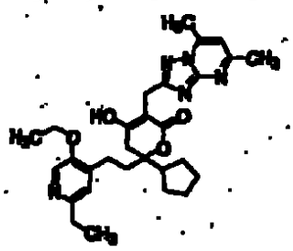
dione. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.08 (t, J=7.3 Hz, 3 H), 1.32 (t, J=6.8 Hz, 3 H), 1.46-1.77 (br m, 8 H), 2.03 (m, 2 H), 2.40 (s, 3 H), 2.44-2.56 (m, 6 H), 2.80 (d, J=17.2 Hz, 1 H), 3.78 (d, J=15.7 Hz, 1 H), 3.83 (d, J=15.7 Hz, 1 H), 3.91 (q, J=7.1 Hz, 2 H), 6.42 (s, 1 H), 6.80 (s, 1 H), 8.73 (s, 1 H), 8.90 (s, 1 H), 9.04 (s, 1 H), 10.98 (s, 1 H). Anal. Calcd. For $C_{28}H_{36}N_2O_6$•0.25 H_2O: C, 68.33; H, 7.01; N, 10.67. Found: C, 68.57; H, 7.07; N, 10.28.

Step 1: 6-Cyclopentyl-6-[2-(2-ethoxy-5-ethyl-4-hydroxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione



The title compound was prepared analogously to step 5 of example A(1) where acetic acid 4-bromo-5-ethoxy-2-ethyl-phenyl ester from step 4 of example A(22) was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of example A(1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (t, J=7.6 Hz, 3 H), 1.38 (t, J=6.8 Hz, 3 H), 1.62-1.85 (br m, 9 H), 1.98 (m, 1 H), 2.33 (m, 1 H), 2.51 (m, 3 H), 2.62 (m, 1 H), 2.73 (d, J=16.2 Hz, 1 H), 2.78 (d, J=16.2 Hz, 1 H), 3.42 (m, 2 H), 3.85 (q, J=7.1 Hz, 2 H), 4.98 (br s, 1 H), 6.33 (s, 1 H), 6.79 (s, 1 H).

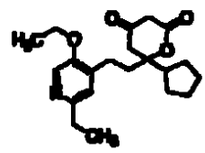
Example A(27): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1) where 6-cyclopentyl-6-[2-(5-ethoxy-2-ethyl-pyridin-4-yl)-ethyl]-dihydro-pyran-2,4-dione from step 1 below was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.19 (t, J=7.6 Hz, 3 H), 1.31 (t, J=6.8 Hz, 3 H), 1.40-1.76 (br m, 8 H), 2.03-2.17 (m, 2 H), 2.48-2.72 (m, 12 H), 2.85 (d, J=17.4 Hz, 1 H), 3.76 (d, J=16.4 Hz, 1 H), 3.87 (d, J=16.2 Hz, 1 H), 4.06 (m, 2 H), 7.09 (m, 2 H), 8.13 (s, 1 H), 10.96 (s, 1 H). MS (ESI): 520.20 $(M+H)^+$

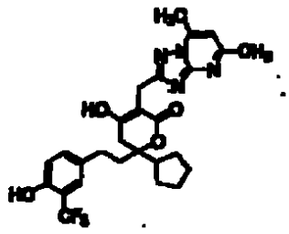
Step 1: 6-Cyclopentyl-6-[2-(5-ethoxy-2-ethyl-pyridin-4-yl)-ethyl]-dihydro-pyran-2,4-dione

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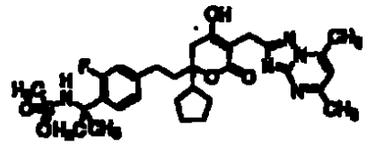
The title compound was prepared analogously to example A(2) where ethyl iodide was substituted in place of methyl iodide in step 1 of that example. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, J=7.8 Hz, 3 H), 1.43 (t, J=6.8 Hz, 3 H), 1.50-2.05 (br m, 9 H), 2.34 (m, 2 H), 2.62-2.77 (m, 6 H), 3.44 (m, 2 H), 4.11 (q, J=6.8 Hz, 2 H), 6.60 (s, 1 H), 8.08 (s, 1 H).

Example A(22): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-hydroxy-3-(trifluoromethyl)phenyl]ethyl]-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(22) where 2-hydroxybenzotrifluoride was substituted in place of 5-ethoxy-2-ethyl-phenol in step 3 of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.39-1.71 (br m, 8 H), 2.09 (m, 2 H), 2.39-2.60 (m, 10 H), 2.77 (d, J=17.7 Hz, 1 H), 3.71 (d, J=16.2 Hz, 1 H), 3.83 (d, J=16.2 Hz, 1 H), 6.86 (d, J=8.6 Hz, 1 H), 7.06 (s, 1 H), 7.29 (s, 1 H), 7.36 (d, J=8.8 Hz, 1 H), 10.29 (s, 1 H), 10.95 (s, 1 H). Anal. Calcd. For $C_{29}H_{36}N_4O_5F_3$•1.0 AcOH: C, 59.57; H, 5.63; N, 9.49. Found: C, 59.13; H, 5.69; N, 9.44.

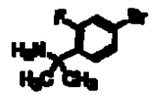
Example A(23): N-[1-[4-[2-[3-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-3-yl]ethyl]-2-fluorophenyl]-1-methylethyl]methanesulfonamide



The title compound was prepared analogously to example A(1) where *N*-[1-(4-bromo-2-fluoro-phenyl)-1-methyl-ethyl]-methanesulfonamide from step 2 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in that example. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.31 - 1.41 (m, 1 H) 1.54 (s, 3 H) 1.55 - 1.70 (m, 5 H) 1.73 (s, 6 H) 1.96 (dd, J=9.96, 7.16 Hz, 2 H) 2.29 - 2.39 (m, 1 H) 2.55 - 2.69 (m, 9 H) 2.73 - 2.81 (m, 4 H) 4.05 (s, 2 H) 5.03 (s, 1 H)

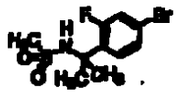
6.84 (t, J=8.69 Hz, 2 H) 6.90 (d, J=8.10 Hz, 1 H) 7.25 (d, J=16.77 Hz, 1 H). MS (ESI): 600 $(M+H)^+$.

Step 1: 1-(4-Bromo-2-fluoro-phenyl)-1-methyl-ethylamine



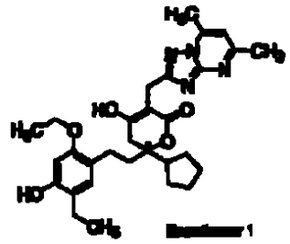
$CeCl_3 \cdot 7H_2O$ (29.7g, 80 mmol) was dehydrated for 2h under vacuum at 160°C. After cooling to 0°C, THF (anhydrous, 640 mL) was added at, and the suspension was stirred for 2h at room temperature. The suspension was cooled to –78°C and MeLi (1.6M in diethylether, 50 mL) was added. The mixture was stirred 30 min, then 4-bromo-2-fluorobenzonitrile (4g, 20 mmol) was added and stirred at that temperature for 5 h. The temperature was raised to 0°C, concentrated NH_4OH (80 mL) was added slowly, and the suspension was filtered though Celite. The aqueous layer was acidified with 1N HCl (aq) and washed with ethyl acetate. The aqueous layer was basified with 3N NaOH (aq) and extracted with dichloromethane. The synthesis and workup were repeated and lots were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a colorless oil (1.25g, 14%). ^1H NMR (300 MHz, $CDCl_3$): δ ppm 1.51 (s, 6 H) 1.69 (s, 2 H) 7.17 - 7.24 (m, 2 H) 7.30 - 7.37 (m, 1 H).

Step 2: *N*-[1-(4-Bromo-2-fluoro-phenyl)-1-methyl-ethyl]-methanesulfonamide



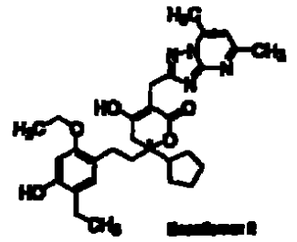
To 1-(4-bromo-2-fluoro-phenyl)-1-methyl-ethylamine(1.2g, 5.4 mmol) and triethylamine (900 µL, 6.5 mmol) in dichloromethane (10 mL) at room temperature was added methanesulfonyl chloride (500 µL, 6.5 mmol). The solution was stirred 16 h, diluted in 1N HCl(aq) and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, then saturated sodium chloride, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to an off-white solid. Flash chromatography (SiO_2, 40% ethyl acetate/hexane) gave a white solid (930 mg, 57%). ^1H NMR (300 MHz, $CDCl_3$): δ ppm 1.76 (s, 6 H) 2.74 (s, 3 H) 4.88 (s, 1 H) 7.24 (d, J=1.51 Hz, 1 H) 7.27 - 7.30 (m, 2 H)

Example A(30): Enantiomer 1 of 8-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethoxy-5-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-6H-pyran-2-one



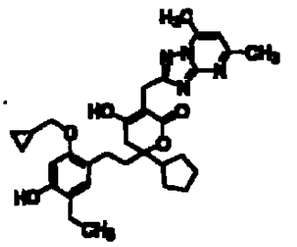
The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethoxy-5-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (120 mg, Example A(22)) using chiral HPLC (Chiralpak AS-H, 115 bar, 55% MeOH). (47 mg, 1.89 min retention time, 100% ee)

Example A(31): Enantiomer 2 of 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethoxy-5-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethoxy-5-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (120 mg, Example A(22)) using chiral HPLC (Chiralpak AS-H, 115 bar, 55% MeOH). (43 mg, 3.429 min retention time, 99% ee)

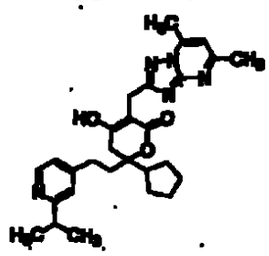
Example A(32): 6-Cyclopentyl-6-[2-[3-(cyclopropylmethoxy)-5-ethyl-4-hydroxyphenyl]ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(22) where (bromomethyl)-cyclopropane was substituted in place of ethyl iodide in step 1 of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.02 (d, J=4.8 Hz, 2 H), 0.28 (d, J=8.6 Hz, 2 H), 0.75 (t, J=7.8 Hz, 3 H), 0.80

(m, 1 H), 1.18-1.51 (br m, 8 H), 1.72 (m, 1 H), 1.82 (m, 1 H), 2.09-2.52 (m, 13 H), 3.41 (d, J=6.8 Hz, 2 H), 3.47 (d, J=15.9 Hz, 1 H), 3.65 (d, J=15.9 Hz, 1 H), 6.08 (s, 1 H), 6.47 (s, 1 H), 6.79 (s, 1 H), 8.70 (s, 1 H), 10.58 (s, 1 H). MS (ESI): 561.25 $(M+H)^+$

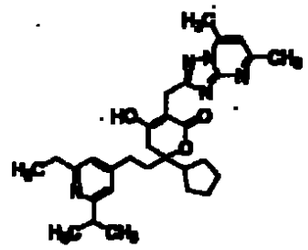
Example A(33): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-(2-isopropylpyridin-4-yl)ethyl]-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(10) where 2-isopropylpyridine was substituted in place of 2,6-bis-(2,2,2-trifluoro-ethyl)-pyridine in step 2 of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.10 (d, J=6.8 Hz, 6 H), 1.29-1.59 (br m, 8 H), 2.03 (m, 2 H), 2.31-2.54 (m, 10 H), 2.67 (d, J=17.4 Hz, 1 H), 2.87 (m, 1 H), 3.60 (d, J=16.2 Hz, 1 H), 3.73 (d, J=16.2 Hz, 1 H), 6.95 (s, 1 H), 7.01 (s, 2 H), 8.25 (d, J=5.8 Hz, 1 H), 10.65 (s, 1 H).

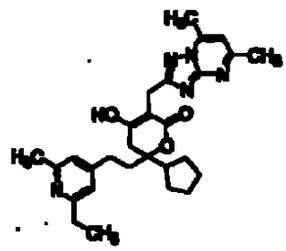
Anal. Calcd. For $C_{32}H_{39}N_5O_4$·0.7EtOAc: C, 67.10; H, 7.42; N, 12.70. Found: C, 67.24; H, 7.61; N, 12.68.

Example A(34): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-6-isopropylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



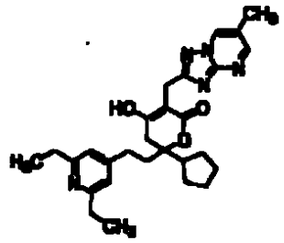
The title compound was prepared analogously to example A(9) where 2-ethyl-6-isopropylpyridine was substituted in place of 2,6-bis-(2,2,2-trifluoro-ethyl)-pyridine in step 2 of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.03 (m, 9 H), 1.24-1.55 (br m, 8 H), 2.00 (m, 2 H), 2.28-2.55 (m, 12 H), 2.68 (d, J=17.4 Hz, 1 H), 2.79 (m, 1 H), 3.57 (d, J=16.2 Hz, 1 H), 3.69 (d, J=16.2 Hz, 1 H), 6.77 (s, 2 H), 6.91 (s, 1 H), 10.79 (s, 1 H). Anal. Calcd. For $C_{33}H_{41}N_5O_4$·0.5AcOH: C, 67.96; H, 7.55; N, 12.78. Found: C, 68.01; H, 7.74; N, 12.77.

Example A(35): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-6-methylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



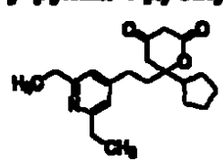
The title compound was prepared analogously to example A(9) where 2-ethyl-6-methylpyridine was substituted in place of 2,6-bis-(2,2,2-trifluoro-ethyl)-pyridine in step 2 of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.83 (d, J=7.3 Hz, 3 H), 1.18-1.47 (br m, 8 H), 1.90 (m, 2 H), 2.15 (s, 3 H), 2.23-2.46 (m, 12 H), 2.56 (d, J=16.9 Hz, 1 H), 3.48 (d, J=16.4 Hz, 1 H), 3.61 (d, J=16.2 Hz, 1 H), 6.68 (s, 1 H), 6.69 (s, 1 H), 6.83 (s, 1 H), 10.67 (s, 1 H). MS (ESI): 490.20 $(M+H)^+$

Example A(26): 6-Cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(4) where 6-cyclopentyl-6-[2-(2-ethoxy-5-ethyl-4-hydroxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione from step 1 below was substituted in place of 6-cyclopentyl-6-[2-(2-ethyl-6-methoxy-pyridin-4-yl)-ethyl]-dihydro-pyran-2,4-dione. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.83 (d, J=7.3 Hz, 6 H), 1.11-1.46 (br m, 8 H), 1.87 (m, 2 H), 2.11 (s, 3 H), 2.21-2.33 (m, 4 H), 2.41 (d, J=7.6 Hz, 4 H), 2.55 (d, J=17.7 Hz, 1 H), 3.48 (d, J=16.2 Hz, 1 H), 3.58 (d, J=16.2 Hz, 1 H), 6.68 (s, 2 H), 6.44 (s, 1 H), 6.61 (s, 1 H), 10.57 (s, 1 H). Anal. Calcd. For $C_{31}H_{39}N_5O_{4.1}$0.5AcOH: C, 67.03; H, 7.13; N, 13.48. Found: C, 67.09; H, 7.25; N, 13.41:

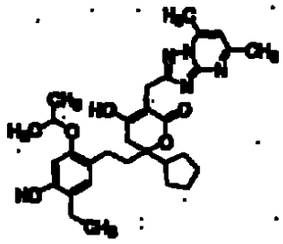
Step 1: 6-Cyclopentyl-6-[2-(2,6-diethyl-pyridin-4-yl)-ethyl]-dihydro-pyran-2,4-dione



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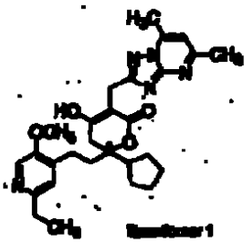
The title compound was prepared analogously to example A(2) where 2,5-diethylpyridine from step 1 of example A(17) was substituted in place 4-bromo-2-ethyl-5-methoxypyridine in step 6 of example A(2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, J=7.8 Hz, 6 H), 1.45-1.78 (br m, 10 H), 1.98 (m, 1 H), 2.28 (m, 2 H), 2.85 (m, 2 H), 2.79 (q, J=7.8 Hz, 4 H), 3.45 (m, 2 H), 6.81 (s, 2 H).

Example A(37): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethyl-4-hydroxy-2-isopropoxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(22) where 2-iodopropane was substituted in place of ethyl iodide in step 1 of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.06 (t, J=7.8 Hz, 3 H), 1.23 (t, J=6.1 Hz, 3 H), 1.28 (t, J=6.1 Hz, 3 H), 1.46-1.85 (br m, 8 H), 1.95 (m, 1 H), 2.11 (m, 1 H), 2.39-2.64 (m, 12 H), 2.80 (d, J=17.4 Hz, 1 H), 3.76 (d, J=15.9 Hz, 1 H), 3.85 (d, J=15.9 Hz, 1 H), 4.40 (m, 1 H), 6.44 (s, 1 H), 6.77 (s, 1 H), 7.09 (s, 1 H), 8.89 (s, 1 H), 10.95 (s, 1 H). Anal. Calcd. For $C_{31}H_{43}N_3O_5$•0.3EtOAc: C, 67.25; H, 7.43; N, 9.74. Found: C, 67.00; H, 7.44; N, 9.72.

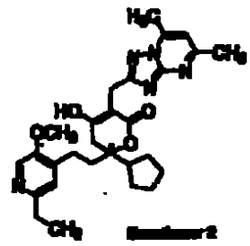
Example A(38): Enantiomer 1 of 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (75 mg, Example A(3)) using chiral HPLC (Chiralpak AD-H, 140 bar, 35% MeOH). (21 mg, 3.758 min retention time, 100% ee)

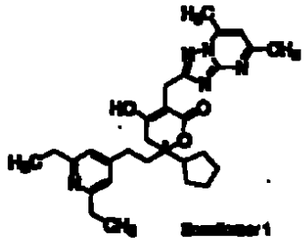
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Example A(39): Enantiomer 2 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



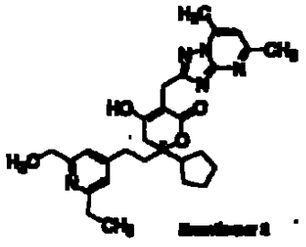
The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (75 mg, Example A(3)) using chiral HPLC (Chiralpak AD-H, 140 bar, 35% MeOH). (21 mg, 8.142 min retention time, 100% ee)

Example A(40): Enantiomer 1 of 6-Cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was separated from racemic 6-cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (80 mg, Example A(17)) using chiral HPLC (Chiralpak AD-H, 140 bar, 35% MeOH). (12 mg, 3.23 min retention time, 100% ee)

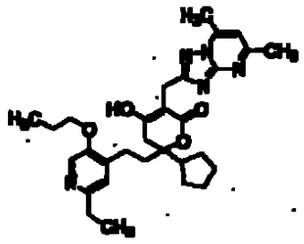
Example A(41): Enantiomer 2 of 6-Cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was separated from racemic 6-cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-

pyran-2-one (80 mg, Example A(17)) using chiral HPLC (Chiralpak AD-H, 140 bar, 35% MeOH). (9 mg, 6.46 min retention time, 100% ee)

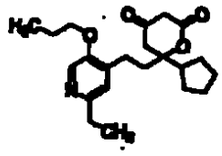
Example A(42): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-propoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1) where 6-cyclopentyl-6-[2-(2-ethyl-5-propoxy-pyridin-4-yl)-ethyl]-dihydro-pyran-2,4-dione from step 1 below was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.06 (t, J=7.3 Hz, 3 H), 1.28 (t, J=7.6 Hz, 3 H), 1.51-1.87 (br m, 10 H), 2.25 (m, 2 H), 2.52-2.91 (m, 13 H), 3.84 (d, J=16.2 Hz, 1 H), 3.94 (d, J=16.2 Hz, 1 H), 4.06 (t, J=6.3 Hz, 2 H), 7.17 (s, 1 H), 8.21 (s, 1 H), 10.98 (s, 1 H), 12.02 (s, 1 H). Anal. Calcd. For $C_{33}H_{42}N_4O_4 \cdot 0.5H_2O$: C, 65.74; H, 7.47; N, 12.78. Found: C, 65.69; H, 7.27; N, 12.80.

Step 1: 6-Cyclopentyl-6-[2-(2-ethyl-5-propoxy-pyridin-4-yl)-ethyl]-dihydro-pyran-2,4-dione

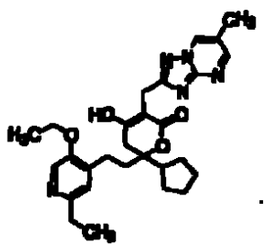


The title compound was prepared analogously to example A(2) where 1-iodopropane was substituted in place of methyl iodide in step 1 of that example.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (t, J=7.3 Hz, 3 H), 1.28 (t, J=7.6 Hz, 3 H), 1.45-1.99 (br m, 12 H), 2.33 (m, 1 H), 2.62-2.76 (m, 6 H), 3.43 (s, 2 H), 3.99 (t, J=6.6 Hz, 2 H), 6.90 (s, 1 H), 8.06 (s, 1 H). Anal. Calcd. For $C_{22}H_{31}NO_4 \cdot 0.5H_2O$: C, 70.07; H, 8.36; N, 3.71. Found: C, 70.10; H, 8.36; N, 3.94.

Example A(43): 6-Cyclopentyl-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-3-[(5-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one

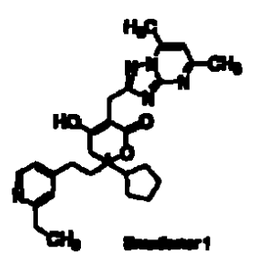
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153



The title compound was prepared analogously to example A(4) where 6-cyclopentyl-6-[2-(5-ethoxy-2-ethyl-pyridin-4-yl)-ethyl]-dihydro-pyran-2,4-dione from step 1 of example A(27) was substituted in place of 6-cyclopentyl-6-[2-(2-ethyl-5-methoxy-pyridin-4-yl)-ethyl]-dihydro-pyran-2,4-dione.

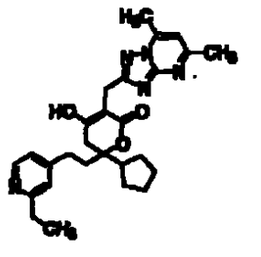
^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.21 (t, J=7.3 Hz, 3 H), 1.34 (t, J=7.8 Hz, 3 H), 1.42-1.79 (br m, 8 H), 2.09 (m, 2 H), 2.41-2.85 (m, 10 H), 3.78 (d, J=16.2 Hz, 1 H), 3.85 (d, J=16.2 Hz, 1 H), 4.11 (q, J=7.8 Hz, 2 H), 7.12 (s, 1 H), 8.15 (s, 1 H), 8.74 (s, 1 H), 8.98 (s, 1 H), 10.94 (s, 1 H).
MS (ESI): 508.20 $(M+H)^+$

Example A(44): Enantiomer 1 of 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



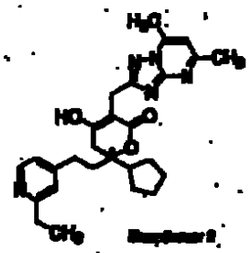
The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (80 mg, from step 1 below) using chiral HPLC (Chiralpak AS-H, 100 bar, 60% MeOH). (28 mg, 1.46 min retention time, 100% ee)

Step 1: 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



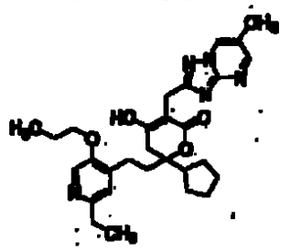
The title compound was prepared analogously to example A(9) where 2-ethylpyridine was substituted in place of 2,6-bis-(2,2,2-trifluoro-ethyl)-pyridine in step 2 of that example.
^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.24 (t, J=7.6 Hz, 3 H), 1.44-1.75 (br m, 8 H), 2.2 (m, 2 H), 2.50-2.88 (m, 13 H), 3.76 (d, J=16.0 Hz, 1 H), 3.89 (d, J=16.0 Hz, 1 H), 7.11 (s, 1 H), 7.16 (s, 2 H), 8.39 (s, 1 H), 11.12 (s, 1 H). MS (ESI): 476.25 ($M+H^+$)

Example A(43): Enantiomer 2 of 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



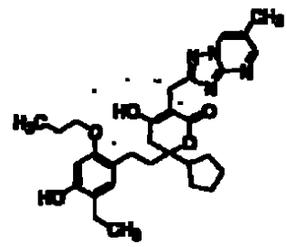
The title compound was separated from racemic 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (80 mg, from step 1 of example A(44)) using chiral HPLC (Chiralpak AS-H, 100 bar, 60% MeOH). (21 mg, 1.83 min retention time, 98.4% ee)

Example A(45): 6-Cyclopentyl-6-[2-(2-ethyl-5-propoxypyridin-4-yl)ethyl]-4-hydroxy-3-[(5-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one



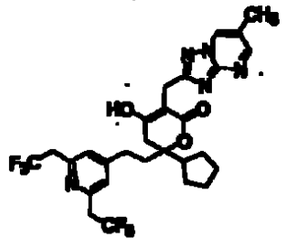
The title compound was prepared analogously to example A(4) where 6-cyclopentyl-6-[2-(2-ethyl-5-propoxy-pyridin-4-yl)-ethyl]-dihydro-pyran-2,4-dione from step 1 of example A(42) was substituted in place of 6-cyclopentyl-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]dihydro-2H-pyran-2,4(3H)-dione.
^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.20 (t, J=7.3 Hz, 3 H), 1.40 (t, J=7.3 Hz, 3 H), 1.81-1.96 (br m, 10 H), 2.29 (m, 2 H), 2.59 (s, 3 H), 2.80-2.90 (m, 6 H), 3.02 (d, J=17.4 Hz, 1 H), 3.87 (d, J=15.9 Hz, 1 H), 4.04 (d, J=15.9 Hz, 1 H), 4.20 (d, J=6.3 Hz, 2 H), 7.30 (s, 1 H), 8.24 (s, 1 H), 8.93 (s, 1 H), 9.14 (s, 1 H), 11.16 (s, 1 H). MS (ESI): 520.20 ($M+H^+$)

Example A(47): 6-Cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxyphenyl)ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(4) where 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione from step 5 of example A(1) below was substituted in place of 6-cyclopentyl-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]dihydro-2H-pyran-2,4(3H)-dione. ^{1}H NMR (400MHz, DMSO-d_6): δ 0.85(t, J=7.3 Hz, 3 H), 0.92 (t, J=7.6 Hz, 3 H), 1.27-1.80 (m, 10 H), 1.88 (m, 2 H), 2.25-2.44 (m, 9 H), 2.84 (d, J=17.7 Hz, 1 H), 3.88 (m, 4 H), 6.27 (s, 1 H), 6.84 (s, 1 H), 8.58 (s, 1 H), 8.74 (s, 1 H), 8.89 (s, 1 H), 10.82 (s, 1 H). Anal. Calcd. For $C_{32}H_{38}N_4O_6$·0.3H_2O: C, 66.72; H, 7.20; N, 10.37. Found: C, 66.55; H, 7.14; N, 10.39.

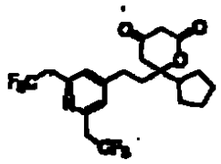
Example A(48): 6-[2-[2,6-Bis(2,2,2-trifluoroethyl)pyridin-4-yl]ethyl]-6-cyclopentyl-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(4) where 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione from step 1 below was substituted in place of 6-cyclopentyl-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]dihydro-2H-pyran-2,4(3H)-dione. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.21-1.56 (br m, 8 H), 1.93 (m, 1 H), 2.08 (m, 1 H), 2.21 (s, 3 H), 2.24-2.58 (m, 4 H), 2.67 (d, J=14.6 Hz, 1 H), 3.58-3.72 (m, 6 H), 7.26 (s, 2 H), 8.53 (s, 1 H), 8.81 (s, 1 H), 10.63 (s, 1 H). MS (ESI): 598.10 $(M+H)^+$

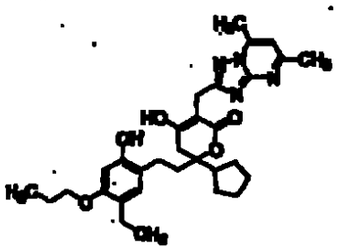
Step 1: 6-[2-[2,6-Bis-(2,2,2-trifluoro-ethyl)-pyridin-4-yl]-ethyl]-6-cyclopentyl-dihydro-pyran-2,4-dione

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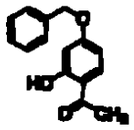
The title compound was prepared analogously to example A(2) where 4-bromo-2,6-bis-(2,2,2-trifluoro-ethyl)-pyridine from step 5 of example A(9) was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41-1.75 (br m, 8 H), 1.98 (m, 2 H), 2.23 (m, 1 H), 2.70 (m, 4 H), 3.44-3.61 (m, 6 H), 7.10 (s, 2 H).

Example A(10): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethyl-2-hydroxy-4-propoxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1) where 6-cyclopentyl-6-[2-(5-ethyl-2-hydroxy-4-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione from step 3 below was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione. ^{1}H NMR (400MHz, DMSO-d_6): δ 1.01 (m, 6 H), 1.42-1.77 (m, 10 H), 1.85 (m, 1 H), 2.15 (m, 1 H), 2.39-2.82 (m, 13 H), 3.70-3.84 (m, 4 H), 6.38 (s, 1 H), 6.75 (s, 1 H), 7.08 (s, 1 H), 9.04 (s, 1 H), 10.13 (s, 1 H). MS (ESI): 549.20 $(M+H)^+$

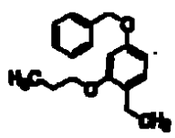
Step 1: 1-(4-Benzyloxy-2-hydroxy-phenyl)-ethanone



Potassium carbonate (54 g, 0.39 mol) followed by benzyl bromide (13.9 mL, 0.12 mol) were added to a solution of 2',4'-dihydroxyacetophenone (20 g, 0.13 mol) in DMF (160mL). The mixture was stirred for 5 hours and then partitioned between H_2O and EtOAc. The organic layer was washed with sat $NaHCO_3$, 1N HCl, brine, dried over Na_2SO_4 and concentrated to a clear oil (28.7g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.56 (s, 3 H), 5.02 (s, 2 H), 6.51 (m, 2 H), 7.33-7.43 (m, 5 H), 7.64 (d, J=8.3 Hz, 1 H), 12.73 (s, 1 H).

Step 2: 4-Benzyloxy-1-ethyl-2-propoxy-benzene

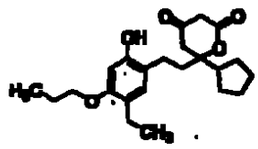
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Potassium carbonate (5.14 g, 12.4 mmol) followed by 1-iodopropane (1.33 mL, 13.6 mmol) were added to a solution of 1-(4-benzyloxy-2-hydroxy-phenyl)-ethanone (3 g, 12.4 mmol) in DMF (30mL). The mixture was stirred for 15 hours and then partitioned between H_2O and EtOAc. The organic layer was washed with 1 N HCl, brine, dried over Na_2SO_4 and concentrated to a pink oil. Purification by flash column chromatography (0% to 20% EtOAc in hexanes) gave a white solid (3.5g, 99%).

The solid was suspended in triethylene glycol (15 mL) and treated with NaOH (1.23 g, 31 mmol) followed by hydrazine monohydrate (1.79 mL, 37 mmol). The mixture was heated to 160 for 16 hours. The reaction mixture was poured into 1 N HCl and extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to a clear oil. Purification by flash column chromatography (0% to 10% EtOAc in hexanes) gave the title compound as a clear oil (2.5g, 76%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (t, J=7.2 Hz, 3 H), 1.16 (t, J=7.6 Hz, 3 H), 1.80 (m, 2 H), 2.58 (q, J=7.6 Hz, 2 H), 3.88 (t, J=6.3 Hz, 2 H), 5.03 (s, 2 H), 6.48 (dd, J=8.1, 2.5 Hz, 1 H), 6.51 (d, J=2.3 Hz, 1 H), 7.09 (d, J=8.1 Hz, 1 H), 7.30-7.44 (m, 5 H).

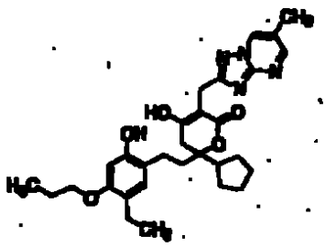
Step 3: 6-Cyclopentyl-6-[2-(5-ethyl-2-hydroxy-4-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione



The title compound was prepared analogously to example A(2) where 4-benzyloxy-1-ethyl-2-propoxy-benzene was substituted in place of 2-benzyloxy-1-ethyl-4-propoxy-benzene in step 3 of that example. ^1H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, J=7.6 Hz, 3 H), 1.18 (m, 6 H), 1.43-2.05 (m, 10 H), 2.50-2.82 (m, 6 H), 3.44 (m, 2 H), 3.84 (m, 2 H), 4.90 (s, 1 H), 6.27 (s, 1 H), 6.79 (s, 1 H).

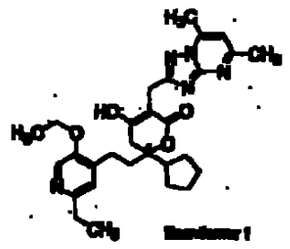
Example A(50): 6-Cyclopentyl-6-[2-(5-ethyl-2-hydroxy-4-propoxyphenyl)ethyl]-4-hydroxy-3-[(3-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one

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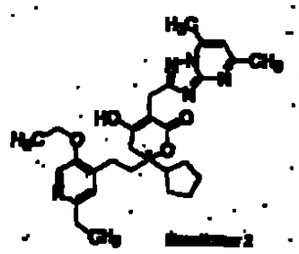
The title compound was prepared analogously to example A(4) where 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione from step 3 of example A(49) was substituted in place of 6-cyclopentyl-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]dihydro-2H-pyran-2,4(3H)-dione. ^{1}H NMR (400MHz, DMSO-d_6): δ 0.85 (m, 6 H), 1.25-1.92 (m, 10 H), 1.83 (m, 2 H), 2.19 (s, 3 H), 2.25-2.65 (m, 7 H), 3.61 (m, 2 H), 3.67 (t, *J*=7.6 Hz, 2 H), 6.23 (s, 1 H), 6.61 (s, 1 H), 6.63 (s, 1 H), 6.70 (s, 1 H), 6.90 (s, 1 H), 10.70 (s, 1 H). MS (ESI): 535.20 $(M+H)^+$

Example A(51): Enantiomer 1 of 9-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (85 mg, Example A(27)) using chiral HPLC (Chiralpak AD-H, 140 bar, 30% MeOH). (22 mg, 5.39 min retention time, 100% ee)

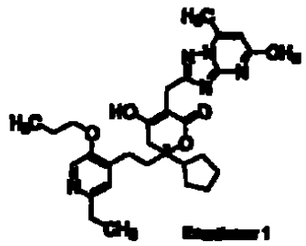
Example A(52): Enantiomer 2 of 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



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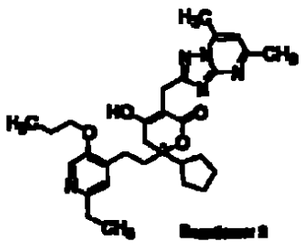
The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (85 mg, Example A(27)) using chiral HPLC (Chiralpak AD-H, 140 bar, 30% MeOH). (16 mg, 7.21 min retention time, 100% ee)

Example A(53): Enantiomer 1 of 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-propoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-propoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (80 mg, Example A(42)) using chiral HPLC (Chiralpak AD-H, 140 bar, 25% MeOH w/ 0.1% isopropylamine). (27 mg, 6.91 min retention time, 100% ee)

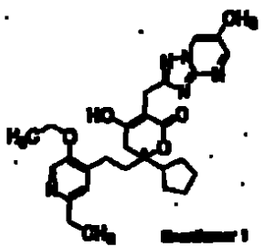
Example A(54): Enantiomer 2 of 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-propoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-propoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (80 mg, Example A(42)) using chiral HPLC (Chiralpak AD-H, 140 bar, 25% MeOH w/ 0.1% isopropylamine). (12.3 mg, 8.91 min retention time, 100% ee)

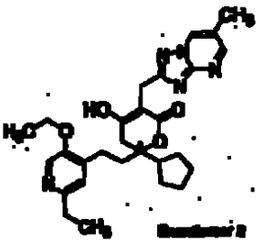
Example A(55): Enantiomer 1 of 6-Cyclopentyl-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one

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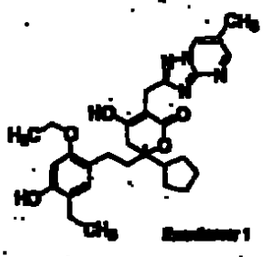
The title compound was separated from racemic 6-cyclopentyl-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one (38 mg, Example A(43)) using chiral HPLC (Chiralpak AD-H, 140 bar, 30% MeOH). (9 mg, 5.49 min retention time, 100% ee).

Example A(56): Enantiomer 2 of 6-Cyclopentyl-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one



The title compound was separated from racemic 6-cyclopentyl-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one (38 mg, Example A(43)) using chiral HPLC (Chiralpak AD-H, 140 bar, 30% MeOH). (9.5 mg, 6.79 min retention time, 100% ee).

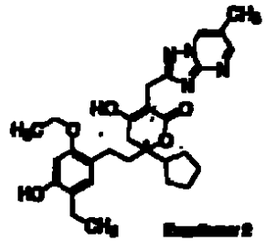
Example A(57): Enantiomer 1 of 6-Cyclopentyl-6-[2-(2-ethoxy-5-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one



The title compound was separated from racemic 6-cyclopentyl-6-[2-(2-ethoxy-5-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-

dihydro-2H-pyran-2-one (70 mg, Example A(25)) using chiral HPLC (Chiralpak AS-H, 140 bar, 40% MeOH w/ 0.1% isopropylamine). (28 mg, 1.73 min retention time, 100% ee).

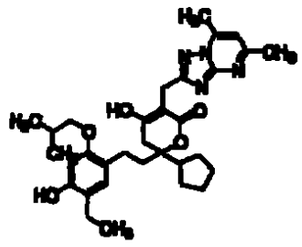
Example A(88): Enantiomer 2 of 6-Cyclopentyl-6-[2-(2-ethoxy-5-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-3-[(5-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one



Enantiomer 2

The title compound was separated from racemic 6-cyclopentyl-6-[2-(2-ethoxy-5-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-3-[(5-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one (70 mg, Example A(25)) using chiral HPLC (Chiralpak AS-H; 140 bar, 40% MeOH w/ 0.1% isopropylamine). (27 mg, 9.35 min retention time, 100% ee).

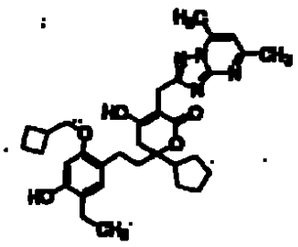
Example A(89): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethyl-4-hydroxy-2-isobutoxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1), where 1-iodo-2-methyl-propane was substituted in place of 1-iodopropane in step 1 of that example. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.00(d, J=6.8 Hz, 6 H), 1.17(t, J=7.6 Hz, 3 H), 1.35-1.78 (m, 12 H), 1.97 (t, J=8.5 Hz, 2 H), 2.07 (m, 1 H), 2.35-2.77 (m, 10 H), 3.61 (d, J=6.3 Hz, 2 H), 4.04 (d, J=15.4 Hz, 1 H), 4.13 (d, J=15.4 Hz, 1 H), 6.30 (s, 1 H), 6.62 (s, 1 H), 6.84 (s, 1 H), 10.72 (s, 1 H).

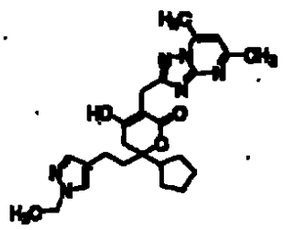
Example A(90): 6-[2-[2-(Cyclobutylmethoxy)-5-ethyl-4-hydroxyphenyl]ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one

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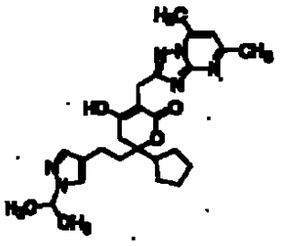
The title compound was prepared analogously to example A(1), where iodomethyl-cyclobutane was substituted in place of 1-iodopropane in step 1 of that example. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.16 (t, J=7.6 Hz, 3 H), 1.35-2.45 (m, 21 H), 2.36-2.78 (m, 10 H), 3.83 (d, J=6.5 Hz, 2 H), 4.07 (d, J=15.4 Hz, 1 H), 4.12 (d, J=15.4 Hz, 1 H), 6.31 (s, 1 H), 6.81 (s, 1 H), 6.84 (s, 1 H), 10.72 (s, 1 H).

Example A(61): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(1-ethyl-1H-pyrazol-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1), where 1-ethyl-4-iodo-1H-pyrazole (ref: Trofimenko, S. *J. Am. Chem Soc 88*, 558,. 1966) was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (400MHz, DMSO-d_6): δ 1.36 (t, J=7.4 Hz, 3 H), 1.57-1.89(m 6 H), 2.10-2.16 (m, 2 H), 2.39-2.79 (m, 11 H), 3.94 (brm, 2 H), 3.74 (d, J=16.5 Hz, 1 H), 3.85 (d, J=16.5 Hz, 1 H), 4.01-4.12 (m, 1 H), 7.02 (s, 1 H), 7.24 (s, 1 H), 7.59 (s, 1 H), 8.26 (s, 1 H), 10.76 (s, 1 H).

Example A(62): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-(1-isopropyl-1H-pyrazol-4-yl)ethyl]-5,6-dihydro-2H-pyran-2-one

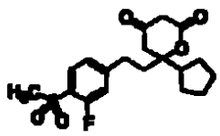


The title compound was prepared analogously to example A(1)b, where 4-iodo-1-isopropyl-1H-pyrazole (ref: Trofimenko, S. *J. Am. Chem Soc 88*, 558,. 1966) was substituted in

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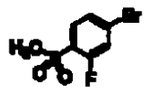
place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (400MHz, DMSO-d_6): δ 1.39 (d, J=6.6 Hz, 6 H), 1.57-1.72(m, 6 H), 2.10-2.17 (m, 3 H), 2.39-2.79 (m, 11 H), 3.74 (d, J=16.2 Hz, 1 H), 3.86 (d, J=16.2 Hz, 1 H), 4.42-4.48 (m, 1 H), 7.00 (s, 1 H), 7.23 (s, 1 H), 7.58 (s, 1 H), 8.23 (s, 1 H), 10.74 (s, 1 H).

Example A(63): 6-Cyclopentyl-6-[2-[3-fluoro-4-(methylsulfonyl)phenyl]ethyl]dihydro-2H-pyran-2,4(3H)-dione



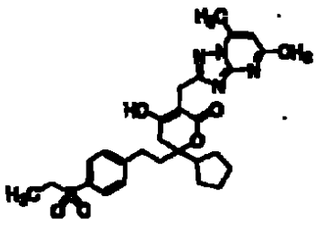
The title compound was prepared analogously to example A(2), where 4-bromo-2-fluoro-1-methanesulfonyl-benzene from step 1 below was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example. ^{1}H NMR ($CDCl_3$): δ 1.42-1.85 (brm, 8H), 1.97 (m, 2H), 2.29 (t, J = 7.9 Hz, 1H), 2.79 (m, 4H), 3.44 (s, 3H), 3.45 (s, 2H), 7.11 (s, 1 H), 7.44 (m, 2 H)

Step 1: 4-Bromo-2-fluoro-1-methanesulfonyl-benzene



The title compound was prepared analogously to step 1 of example B(2), where 4-bromo-2-fluorobenzenesulfonyl chloride was used in place of 4-bromo-2-chlorobenzenesulfonyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.34 (s, 3 H), 7.57 (d, J=8.5, 2 H), 7.76 (d J=8.5 2 H), 8.14 (s, 1 H)

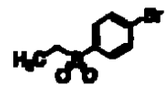
Example A(64): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-{2-[4-(ethylsulfonyl)phenyl]ethyl}-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1), where 1-bromo-4-ethanesulfonyl-benzene from step 1 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.37 (t, J=7.5 Hz, 3 H) 1.40-2.19 (m, 13 H), 2.58 (s, 3 H), 2.73 2.99(m, 7 H), 3.02 (q, J=12.57 Hz, 2 H), 5.99 (s, 1 H), 7.28 (dd, J=3.56 Hz, 2 H), 7.70 (dd, J=3.06 Hz, 1 H). Anal. Calcd. For $C_{28}H_{34}N_4O_5S$: C, 62.43; H, 6.36; N, 10.40. Found: C, 62.25; H, 6.40; N, 10.34.

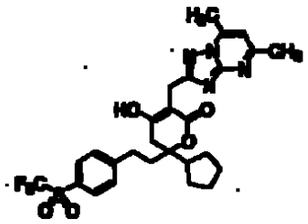
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Step 1: Bromo-4-ethanesulfonyl-benzene



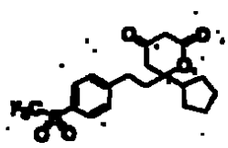
1-Bromo-4-ethylsulfanyl-benzene (5.0 g) was dissolved in acetic acid and potassium permanganate as a 3% solution in water (8 mL) was added. The reaction mixture was heated to 90°C for 3hrs, after which time the reaction was cooled to room temperature and partitioned between ethyl acetate and 2N NaOH solution (500 m) each. The organics were separated and washed with water (100 mL), dried over sodium sulfate and purified on biotage eluting with 90:10 hexanes : ethyl acetate to afford the title compound as a clear oil (2.70 g). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.30 (t, J=7.85 Hz, 3 H) 3.02 (q, J=7.54 Hz, 2 H), 7.40 (m, 4 H).

Example A(88): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-(2-{4-[(trifluoromethyl)sulfonyl]phenyl}ethyl)-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1), where 6-cyclopentyl-6-(2-{4-[(trifluoromethyl)sulfonyl]phenyl}ethyl)dihydro-2H-pyran-2,4(3H)-dione (Example A(88) was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione in that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.35-2.23 (m, 11 H), 2.58 (s, 3 H), 2.73-2.89(m, 7 H), 3.03 (t, J=8.57 Hz, 2 H), 6.99 (s, 1 H), 7.78 (d, J=2.56 Hz, 2 H), 8.10 (dd, J=2.36 Hz, 2 H) Anal. Calcd. For $C_{27}H_{29}N_4O_6S$: C, 56.04; H, 5.05; N, 9.68. Found: C, 56.35; H, 5.20; N, 9.34.

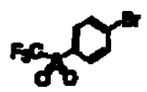
Example A(89): 6-Cyclopentyl-6-(2-{4-[(trifluoromethyl)sulfonyl]phenyl}ethyl)dihydro-2H-pyran-2,4(3H)-dione



The title compound was prepared analogously to example A(2), where 1-bromo-4-trifluoromethanesulfonyl-benzene from step 1 below was substituted in place of (4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.35-2.33 (m, 11 H), 2.80-3.15 (m, 6 H), 7.75 (d, J=1.56 Hz, 2 H), 8.10 (d, J=1.56 Hz, 2 H).

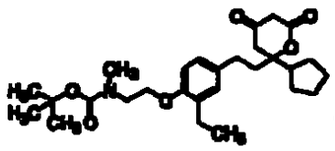
Step 1: 1-Bromo-4-trifluoromethanesulfonyl-benzene

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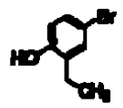
The title compound was prepared analogously to step 1 from example A(84), where 1-bromo-4-trifluoromethylsulfanyl-benzene was substituted in place of 1-bromo-4-ethylsulfanyl-benzene in step 1 of that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.80-7.93 (m, 4 H).

Example A(87):tert-Butyl 2-(4-[2-(3-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-3-ethylphenoxy)ethyl(methyl)carbamate



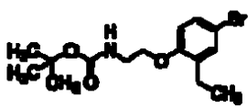
The title compound was prepared analogously to example A(2), where [2-(4-bromo-2-ethyl-phenoxy)-ethyl]-methyl-carbamic acid tert-butyl ester from step 3 below was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.16 (t, J=7.58 Hz, 3 H) 1.40-2.25 (m, 20 H), 2.62-3.13 (m, 14 H), 3.42 (q, J=6.54 Hz, 2 H), 3.84 (t, J=7.54 Hz, 2 H), 6.58 (d, J=2.06 Hz, 1 H), 6.69 (d, J=1.58 Hz, 1 H), 6.94 (s, 1 H).

Step 1: 4-Bromo-2-ethyl-phenol



A solution of tetrabutyl ammonium tribromide (39.58 g, 0.08mol) in $CHCl_3$ (100 mL) was added to a stirred solution of 2-ethyl-phenol (10.0 g, 0.08 mol) dissolved in $CHCl_3$ (100 mL). The reaction mixture was stirred for 2 hrs and then quenched with 5% solution of sodium thiosulfate (100 mL). The biphasic mixture was stirred for 30 mins and then the layers were separated. The organic layer was washed with 1 N HCl, brine, dried over Na_2SO_4 and concentrated to a red oil. Purification by flash column chromatography (0% to 15% EtOAc in hexanes) gave the product as an oil (14 g.). LCMS : APCI –VE=200 M/E.

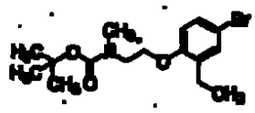
Step 2: [2-(4-Bromo-2-ethyl-phenoxy)-ethyl]-carbamic acid tert-butyl ester



4-Bromo-2-ethyl-phenol (1.75g, 8.70mmol) from step 1 above was dissolved in acetonitrile (10ml) and cesium carbonate (2.83g, 8.70mmol) was added followed by (2-Bromo-ethyl)-carbamic acid tert-butyl ester (1.95g, 8.70mmol). The reaction was stirred at room temperature for

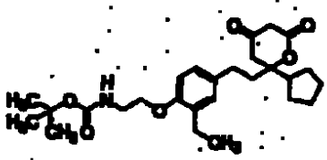
18hrs. The mixture was partitioned between ethyl acetate (200ml) and water (200ml), the organics were separated and dried over magnesium sulfate and concentrated to a oil. Purification by flash column chromatography (0% to 30% EtOAc in hexanes) gave the product as an oil (1.0 g.). LCMS : APCI +VE=244 M/E, mass – BOC.

Step 2: [2-(4-Bromo-2-ethyl-phenoxy)-ethyl]-methyl-carbamic acid tert-butyl ester



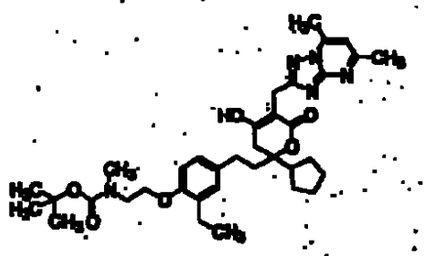
2-(4-Bromo-2-ethyl-phenoxy)-ethyl]-carbamic acid tert-butyl ester (1.0g, 2.90mmol) was dissolved in THF (50ml) and 60% NaH (128mg, 3.19mmol) was added followed by methyl iodide (0.2ml, 3.19mmol). The reaction was stirred at room temperature for 18hrs. The mixture was partitioned between ethyl acetate (100ml) and water (100ml), the organics were separated and dried over magnesium sulfate and concentrated to a clear oil. (1.3 g). LCMS : electrospray +VE=380 M/E, mass + sodium.

Example A(66): tert-Butyl 2-(4-[2-(2-cyclopentyl-4,5-dioxotetrahydro-2H-pyran-3-yl)ethyl]-3-ethylphenoxy)ethylcarbamate



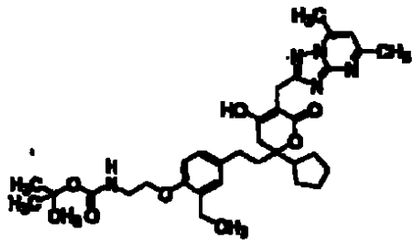
The title compound was prepared analogously to example A(2), where [2-(4-bromo-2-ethyl-phenoxy)-ethyl]carbamic acid tert-butyl ester from step 2 of example A(57) was substituted in place of4-bromo-2-ethyl-5-methoxy-pyridinein step 6 of that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.16 (t, J=7.56 Hz, 3 H) 1.40-2.22 (m, 20 H), 2.60-3.10 (m, 11 H), 3.39 (q, J=6.54 Hz, 2 H), 3.84 (t, J=7.54 Hz, 2 H), 6.58 (d, J=2.06 Hz, 1 H), 6.64 (d, J=1.58 Hz, 1 H), 6.94 (s, 1 H).

Example A(68): tert-Butyl 2-[4-(2-(2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-5,6-dihydro-2H-pyran-3-yl)ethyl)-3-ethylphenoxy]ethyl(methyl)carbamate



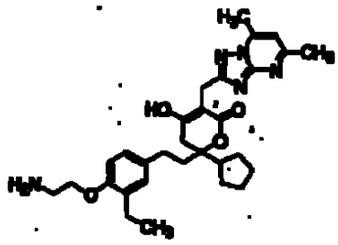
The title compound was prepared analogously to example A(1), where tert-butyl 2-{4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-ethylphenoxy}ethyl(methyl)carbamate (Example A(67)) was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione in that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.20 (t, J=6.56 Hz, 3 H) 1.40-2.30 (m, 20 H), 2.55-2.99 (m, 17 H), 3.35 (q, J=6.54 Hz, 2 H), 3.90 (t, J=7.54 Hz, 3 H), 6.60 (d, J=1.56 Hz, 1 H), 6.67 (d, J=1.56 Hz, 1 H), 7.00 (m, 2 H). Anal. Calcd. For $C_{38}H_{49}N_5O_6$: C, 66.74; H, 7.52; N, 10.51. Found: C, 66.50; H, 7.40; N, 10.84.

Example A(70): tert-Butyl 2-{4-(2-[2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-5,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenoxy}ethylcarbamate



The title compound was prepared analogously to example A(1), where tert-butyl 2-{4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-ethylphenoxy}ethylcarbamate (Example A(68)) was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione in that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.20 (t, J=6.56 Hz, 3 H) 1.40-2.30 (m, 20 H), 2.55-2.99 (m, 15 H), 3.35 (q, J=6.54 Hz, 2 H), 3.90 (t, J=7.54 Hz, 3 H), 6.60 (d, J=1.56 Hz, 1 H), 6.67 (d, J=1.56 Hz, 1 H), 7.00 (m, 2 H). Anal. Calcd. For $C_{36}H_{47}N_5O_6$: C, 66.33; H,7.47; N, 11.05. Found: C, 66.30; H, 7.40; N, 11.10.

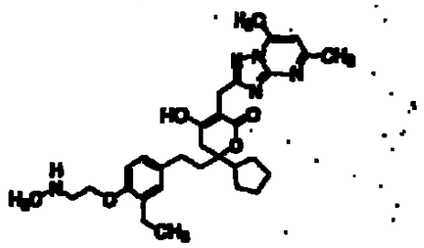
Example A(71): 6-[2-[4-(2-Aminoethoxy)-3-ethylphenyl]ethyl]-6-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



tert-Butyl 2-(4-(2-[2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-5,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenoxy}ethylcarbamate (Example A(70)) (250mg) was dissolved in 4N HCl in dioxane (10ml) and stirred at room temperature for 12hrs. Upon completion the mixture was concentrated and azeotroped several times with

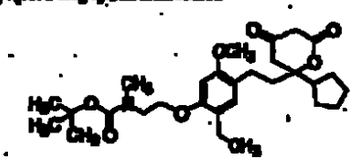
dichloromethane to afford the title compound as a white solid (235mg). ^{1}H NMR (300MHz, MeOD): δ 1.18 (t, J=7.56 Hz, 3 H) 1.32-2.25 (m, 11 H), 2.69-2.85 (m, 15 H), 2.92 (dd, J=16.54 Hz, 1 H), 4.05 (t, J=7.54 Hz, 2 H), 6.55 (d, J=1.56 Hz, 1 H), 6.65 (d, J=1.56 Hz, 1 H), 6.95 (s, 1 H), 6.99 (s, 1 H).

Example A(72): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-(2-[2-ethyl-4-[2-(methylamino)ethoxy]phenyl]ethyl)-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(71) where *tert*-butyl 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-ethylphenoxy]ethyl(methyl)carbamate (Example A(69)) was substituted in place of tert-butyl 2-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-ethylphenoxy]ethylcarbamate in that example. ^{1}H NMR (300MHz, MeOD): δ 1.16 (t, J=6.54 Hz, 3 H) 1.32-2.35 (m, 11 H), 2.40 (s, 3H), 2.59-2.75 (m, 14 H), 2.92 (t, J=16.54 Hz, 2 H), 3.84 (t, J=7.54 Hz, 2 H), 6.55 (d, J=2.06 Hz, 1 H), 6.65 (d, J=2.56 Hz, 1 H), 6.95 (m, 2 H).

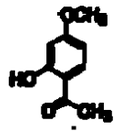
Example A(73): tert-Butyl 2-[4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-ethyl-5-methoxyphenoxy]ethyl(methyl)carbamate



The title compound was prepared analogously to example A(2), where [2-(4-bromo-5-methoxy-2-ethyl-phenoxy)-ethyl]carbamic acid tert-butyl ester from step 5 below was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.16 (t, J=7.56 Hz, 3 H) 1.40-2.25 (m, 20 H), 2.62-3.13 (m, 14 H), 3.42 (q, J=6.54 Hz, 2 H), 3.84 (t, J=7.54 Hz, 2 H), 4.00 (s, 3 H) 6.28 (s, 1 H), 6.96 (s, 1 H).

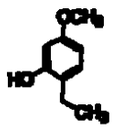
Step 1: 1-(4-Methoxy-2-hydroxy-phenyl)-ethanone

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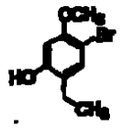
Potassium carbonate (27.2 g, 197 mmol) followed by methyl iodide (4.1 mL, 65.7 mmol) were added to a solution of 2',4'-dihydroxyacetophenone (10.0 g, 65.7 mmol) in DMF (100mL). The mixture was stirred for 4 hours and then partitioned between H_2O and EtOAc. The organic layer was washed with satd $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated to a clear oil (11.0g). ^1H NMR (300MHz, $CDCl_3$): δ 2.60- (s, 3 H), 3.80 (s, 3 H), 6.40 (s, 1 H) 6.51 (d, J=2.45 Hz, 1 H), 7.82 (d, J=8.67 Hz, 1 H), 12.90 (s, 1 H).

Step 2: 5-Methoxy-2-ethyl-phenol



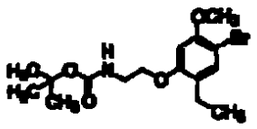
1-(4-Methoxy-2-hydroxy-phenyl)-ethanone (11.0g) was dissolved in MeOH (100 mL), treated with 10 wt % Pd/C (4.0g, Degussa type) and stirred under a balloon of H_2 for 24 hours. The reaction mixture was filtered through a pad of celite washing with EtOAc. The filtrate was concentrated to give the product as an oil (10.0 g). ^1H NMR (300MHz, $CDCl_3$): δ 1.20 (t, J=7.55 Hz, 3 H) 2.60- (q, J=8.22 Hz 2 H), 3.75 (s, 3 H), 6.40 (dd, J=8.04Hz, 2.64 Hz, 1 H), 6.45 (d, J=2.64 Hz, 1 H) 7.00 (d, J=8.29 Hz, 1 H), 12.90 (s, 1 H).

Step 3: 4-Bromo-5-methoxy-2-ethyl-phenol (



A solution of tetrabutyl ammonium tribromide (38.10g, 79 mmol) in $CHCl_3$ (100 mL) was added to a stirred solution of 5-methoxy-2-ethyl-phenol (12.0g, 79mmol) dissolved in $CHCl_3$ (90 mL). The reaction mixture was stirred for 4hrs and then quenched with 5% solution of sodium thiosulfate (90 mL). The biphasic mixture was stirred for 30 mins and then the layers were separated. The organic layer was washed with 1 N HCl, brine, dried over Na_2SO_4 and concentrated to a red oil. Purification by flash column chromatography (0% to 60% EtOAc in hexanes) gave the product as an oil (19g). LCMS : APCI –VE=230 M/E.

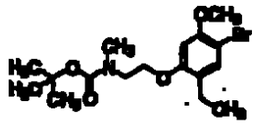
Step 4: [2-(4-Bromo-5-methoxy-2-ethyl-phenoxy)-ethyl]-carbamic acid tert-butyl ester



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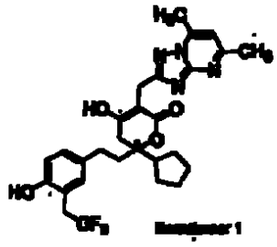
4 Bromo-5-methoxy-2-ethyl-phenol (10.0g, 43mmol) from step 3 above was dissolved in DMF (100ml) and cesium carbonate (21.17g, 65mmol) was added followed by (2-bromo-ethyl)-carbamic acid tert-butyl ester (21.17g, 65mmol). The reaction was stirred at room temperature for 16hrs. The mixture was partitioned between ethyl acetate (200ml) and 10% citric acid (200ml), the organics were separated and dried over magnesium sulfate and concentrated to a oil. Purification by flash column chromatography (0% to 30% EtOAc in hexanes) gave the product as an oil (10.0 g.). LCMS : APCI +VE=375 M/E.

Step 5: [2-(4-Bromo-5-methoxy-2-ethyl-phenoxy)-ethyl]-methyl-carbamic acid tert-butyl ester



2-(4-Bromo-5-methoxy-2-ethyl-phenoxy)-ethyl]-carbamic acid tert-butyl ester (5.0g, 13.4mmol) was dissolved in THF (50ml) and 60% NaH (804mg, 20.1mmol) was added followed by methyl iodide (1.3ml, 20.1mmol). The reaction was stirred at room temperature for 16hrs. The mixture was partitioned between ethyl acetate (100ml) and 1N citric acid (100ml), the organics were separated and dried over magnesium sulfate and concentrated to a clean oil. (5.0g). LCMS : APCI +VE=389 M/E.

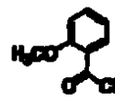
Example A(74): Enantiomer 1 of 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-hydroxy-3-(2,2,2-trifluoroethyl)phenyl]ethyl]-5,6-dihydro-2H-pyran-2-one



Enantiomer 1

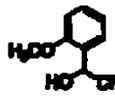
The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-hydroxy-3-(2,2,2-trifluoroethyl)phenyl]ethyl]-5,6-dihydro-2H-pyran-2-one (100mg, from step 9 below) using chiral HPLC (Chiralpak AS-H, 100 bar, 30% MeOH). (26 mg, 1.677 min retention time, 100% ee)

Step 1: 2,2,2-trifluoro-1-(2-methoxyphenyl)ethanone.



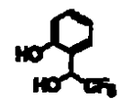
2 Methoxy phenyl magnesium bromide (35ml) was added slowly to a solution of methyl trifluoroacetate (5.0g) in diethyl ether (100ml) at -78°C. The reaction mixture was warmed to room temperature over 12hrs and the quenched with saturated ammonium chloride solution (100ml). The mixture was then partitioned between ethyl acetate (500ml) and water (250ml) The organics were separated and dried over magnesium sulfate filtered and concentrated in vacuuo. The crude residue was purified by column chromatography on silica gel eluting with 100 % hexanes, 90:10 and 80:20, hexanes:ethyl acetate, to afford title compound as a yellow oil. (4.0g). ^{1}H NMR ($CDCl_3$): δ 3.57 (s, 3H), 7.00 (m, 2H), 7.35 (m,1H), 7.63, (d, J = 2.64 Hz 2H).

Step 2: 2,2,2-trifluoro-1-(2-methoxyphenyl)ethanol.



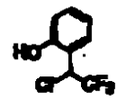
10% Palladium on carbon (1.5g) was added to a solution of 2,2,2-trifluoro-1-(2-methoxyphenyl)ethanone (3.0g) in methanol (50ml). The resultant was hydrogenated at room temperature for 12hrs. After which time the catalyst was filtered off through a plug of celite and the solvent concentrated in vacuuo. The crude was purified by column chromatography on silica gel eluting with 100% hexanes the 80:20 hexanes:ethylacetate to afford the title compound as a yellow oil (3.0g). ^{1}H NMR ($CDCl_3$): δ 3.75 (d, J = 2.56Hz, 1H), 3.96 (s, 3H), 5.35 (m,1H), 7.05 (m, 2H), 7.50 (m,2H).

Step 3: 2-(2,2,2-trifluoro-1-hydroxyethyl)phenol



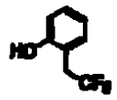
Boron tribromide (10ml) (1M soln in DCM) was added to a solution of 2,2,2-trifluoro-1-(2-methoxyphenyl)ethanol (1.5g) in dichloromethane (20ml). The reaction mixture was stirred at room temperature under a atmosphere of nitrogen for 68hrs. The mixture was then partitioned between DCM (100ml) and 1N HCl (100ml), organics washed with water (100ml), dried over magnesium sulfate, filtered and solvent removed *in vacuuo* to afford the title compound as a clear yellow oil (1.5g). ^{1}H NMR ($CDCl_3$): δ 3.50 (bs, 1H), 5.25 (m, 1H), 6.73 (bs, 1H), 7.00 (m, 2H), 7.32 (d, J = 2.56Hz, 1H), 7.45 (m, 1H).

Step 4: 2-(1-chloro-2,2,2-trifluoroethyl)phenol



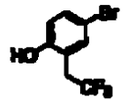
Thionyl chloride (2.28ml) was added to a solution of 2-(2,2,2-trifluoro-1-hydroxyethyl)phenol (3.0g) and pyridine (1.23ml) in toluene (30ml). The reaction was stirred at room temperature for 1hr, after which time the toluene was removed *in vacuuo* and the residue partitioned between ethyl acetate (100ml) and 1N HCl (100ml). The organics were separated and dried over magnesium sulfate, filtered and solvent removed *in vacuuo* to afford the title compound as a clear oil (3.0g). ^{1}H NMR ($CDCl_3$): δ 5.93 (m, 1H), 6.90 (d, J = 4.52Hz, 1H), 7.10 (m, 1H), 7.35 (m, 1H), 7.69 (m, 1H).

Step 5: 2-(2,2,2-trifluoroethyl)phenol



Sodium borohydride (.930g) was added to a solution of 2-(1-chloro-2,2,2-trifluoroethyl)phenol (2.6g) in THF (30ml). The reaction mixture was then stirred for 14hrs at room temperature under an atmosphere of nitrogen, after which time the reaction was quenched with 1N HCl (50ml) and partitioned between 1N HCl (100ml) and ethyl acetate (200ml), the organics were separated and dried over magnesium sulfate, filtered and solvent evaporated *in vacuuo* to afford title compound as a semi solid (2.4g). ^{1}H NMR ($CDCl_3$): δ 3.50 (q, J = 21.06Hz 2H), 6.80 (m, 1H), 7.00 (m, 1H), 7.25 (m, 2H).

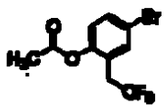
Step 6: 4-bromo-2-(2,2,2-trifluoroethyl)phenol



Tetrabutylammonium tribromide (6.58g) was dissolved in chloroform (50ml) and added dropwise to a solution of 2-(2,2,2-trifluoroethyl)phenol (2.4g) in chloroform (50ml). The reaction mixture was stirred at room temperature for 2hrs, after which time 5% sodium thiosulfate solution (100ml) was added and the resultant stirred for 30mins.The mixture was then partitioned between dichloromethane (100ml) and 1N HCl (200ml). The organics were separated and dried over magnesium sulfate. The solvent was then removed *in vacuuo*, the crude residue was then purified by column chromatography on silica gel eluting with 90:10 hexanes : ethyl acetate to afford the title compound as a yellow oil (3.24g). ^{1}H NMR ($CDCl_3$): δ 3.50 (q, J = 21.48Hz 2H), 6.70 (d, J = 2.54Hz, 1H), 7.32 (d, J = 2.54Hz, 1H), 7.45 (s, 1H).

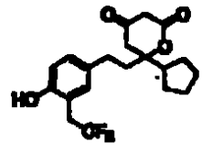
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Step 7: Acetic acid 4-bromo-2-(2,2,2-trifluoro-ethyl)-phenyl ester



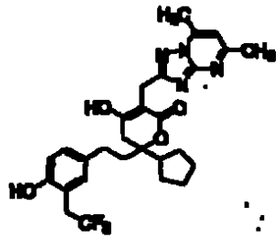
Acetyl chloride (0.91 mL, 12.8 mmol) followed by triethylamine (1.8 mL, 12.8 mmol) were added to a stirred solution of 4-bromo-2-(2,2,2-trifluoroethyl)phenol (2.55 g, 10.7 mmol) dissolved in CH_2Cl_2 (20 mL). The reaction was stirred for 45 mins and then partitioned between 1N HCl and EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine dried over Na_2SO_4 and concentrated. Purification by flash column chromatography (0% to 20% EtOAc in hexanes) gave the product as a clear oil (2.80g). LCMS : apci 297 MH+

Step 8: 6-Cyclopentyl-6-[2-[4-hydroxy-3-(2,2,2-trifluoroethyl)phenyl]ethyl]dihydro-2*H*-pyran-2,4(3*H*)-dione



The title compound was prepared analogously to example A(2) where acetic acid 4-bromo-2-(2,2,2-trifluoro-ethyl)-phenyl ester from step 7 above was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example. ^{1}H NMR ($CDCl_3$): δ 1.35-1.70 (brm, 6H), 1.93, (brm, 2H), 2.04-2.21 (brm, 3H), 2.83-3.12 (brm, 5H), 6.78 (dd, *J* = 2.61 Hz 2H), 6.99 (s, 1H). MS(APCI): 385 (M-H).

Step 9: 6-Cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-hydroxy-3-(2,2,2-trifluoroethyl)phenyl]ethyl]-5,6-dihydro-2H-pyran-2-one

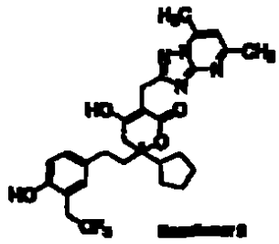


The title compound was prepared analogously to example A(1) where 6-cyclopentyl-6-[2-[4-hydroxy-3-(2,2,2-trifluoroethyl)phenyl]ethyl]dihydro-2*H*-pyran-2,4(3*H*)-dione was substituted in place of 6-cyclopentyl-6-[2-(3-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione in that example. ^{1}H NMR (DMSO): δ 1.40-1.90 (brm, 8H), 1.99-2.28 (brm, 3H), 2.59 (s, 3H), 2.73.(m, 5H), 3.00(m, 2H); 3.10 (m, 2H), 3.47 (m, 3H), 6.79 (m, 2H), 7.05(m, 2H),

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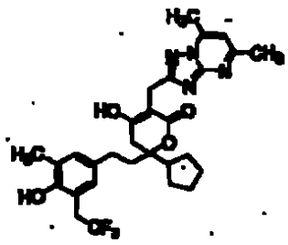
8.83 (bs, 1H), 10.0 (bs; 1H). Anal. Calcd. For $C_{28}H_{31}O_6N_4F_3$: C, 61.76; H, 5.74, N, 10.29. Found: C, 61.50; H, 5.80, N, 10.14.

Example A(78): Enantiomer 2 of 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-hydroxy-3-(2,2,2-trifluoroethyl)phenyl]ethyl]-5,6-dihydro-2H-pyran-2-one



The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-hydroxy-3-(2,2,2-trifluoroethyl)phenyl]ethyl]-5,6-dihydro-2H-pyran-2-one (100mg, from step 9 of example A(74) using chiral HPLC (Chiralpak AS-H, 100 bar, 30% MeOH). (27 mg, 3.566 min retention time, 100% ee)

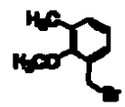
Example A(79):) 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-hydroxy-3-methyl-5-(2,2,2-trifluoroethyl)phenyl]ethyl]-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1) where 2-benzyloxy-5-iodo-1-methyl-3-(2,2,2-trifluoro-ethyl)-benzenefrom step 5 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.35-1.80 (m, 8 H), 2.00-2.40 (m, 6 H), 2.56 (s, 3 H), 2.80 (m, 7 H), 3.10 (t, J=7.06 Hz, 2 H), 3.20 (q, J=10.47 Hz, 2 H) 6.52 (s, 1 H), 6.81 (s, 1 H), 6.99 (s, 1 H), 8.82 (s, 2H). Anal. Calcd. For $C_{29}H_{33}F_3N_4O_4$: C, 62.36; H, 5.95; N, 10.03. Found: C, 62.30; H, 5.83; N, 10.16.

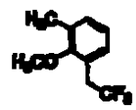
Step 1: 1-Bromomethyl-2-methoxy-3-methyl-benzene

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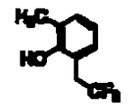
2-5-Dimethylanisole (10.0g, 73mmol) was dissolved in CCl_4 (100ml) and NBS (26.28g, 147mmol) followed by benzoyl peroxide (884mg 5 mol%) were added. The reaction was heated to reflux and stirred as such for 48hrs, after which time the mixture was cooled to room temperature and filtered. The filtrate was concentrated and purified by flash column chromatography (0% to 30% EtOAc in hexanes) to give the product as a white solid (19.9g.). LCMS: APCI –VE=215

Step 2: 2-Methoxy-1-methyl-3-(2,2,2-trifluoro-ethyl)-benzene



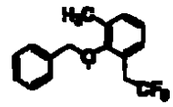
Trimethyl(trifluoromethyl)silane (25.39 mL, 162.5 mmol) was added to a stirred mixture of 1-bromomethyl-2-methoxy-3-methyl-benzene(18g, 65 mmol), KF (9.44g, 162.5 mmol), CuI (37.10g, 195 mmol) in DMF (75 mL) and NMP (75 mL). The reaction mixture was heated to 55 °C under N_2 for 15 hours. The mixture was poured into water, made basic with 1N NaOH and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to a black oil. Flash column chromatography (0% to 60% EtOAc in hexanes) gave the product as a yellow oil (12.0g). LCMS: APCI –VE=203

Step 3: 2-Methyl-6-(2,2,2-trifluoro-ethyl)-phenol



2-Methoxy-1-methyl-3-(2,2,2-trifluoro-ethyl)-benzene(6.0g) was dissolved in dichloromethane (100ml) and BBr_3 (100ml) added. The reaction was allowed to stir at room temperature for 12hrs, after which time it was quenched slowly with cHCl. The mixture was then made basic with 2N NaOH solution and the organics discarded. The aqueous was acidified with 1N HCl and the product extracted with ethyl acetate to afford the title compound as a brown oil (4.43g). LCMS: APCI –VE=189

Step 4: 2-Benzyloxy-1-methyl-3-(2,2,2-trifluoro-ethyl)-benzene

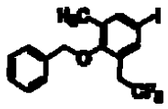


Potassium carbonate (953mg, 6.89 mmol) followed by benzyl bromide (0.8 mL, 6.89 mmol) were added to a solution of 2-methyl-6-(2,2,2-trifluoro-ethyl)-phenol (1.78 g, 6.89 mmol) in DMF (20mL). The mixture was stirred at room temperature for 15 hours and then partitioned

M75
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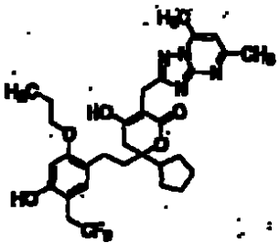
between H_2O and EtOAc. The organic layer was washed with 1N HCl, brine, dried over Na_2SO_4 and concentrated to a brown oil. Purification by flash column chromatography (0% to 20% EtOAc in hexanes) gave the product as a clear oil (2.1g). LCMS: APCI –VE=279

Step B: 2-Benzyloxy-5-iodo-1-methyl-3-(2,2,2-trifluoro-ethyl)-benzene



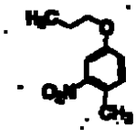
A solution of iodine (1.52g, 6.0 mmol) dissolved in $CHCl_3$ (30 mL) was added dropwise to a stirred mixture of 2-benzyloxy-1-methyl-3-(2,2,2-trifluoro-ethyl)-benzene (2.1g, 6.0 mmol), silver trifluoroacetate (1.33g, 6.0mmol) in $CHCl_3$ (20 mL). After the addition was complete the reaction mixture was stirred for 1 hour. The mixture was filtered through a pad of celite washing with CH_2Cl_2. The filtrate was washed with sold $Na_2S_2O_3$, brine, dried over Na_2SO_4 and concentrated to a pale yellow solid (1.66g). LCMS: APCI –VE=405

Example A(77):) 8-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-hydroxy-3-propoxy-5-(2,2,2-trifluoroethyl)phenyl]ethyl]-5,6-dihydro-6H-pyran-2-one



The title compound was prepared analogously to example A(1), where 1-benzyloxy-4-iodo-5-propoxy-2-(2,2,2-trifluoro-ethyl)-benzenefrom step 4 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^1H NMR (300MHz, $CDCl_3$): 0.98 (t, J=6.79 Hz, 3 H) 1.40-2.40 (m, 10 H), 2.50-2.75 (m, 10 H), 3.10 (q, J=10.08 Hz, 2 H), 3.78 (t, J=6.56 Hz, 2 H) 6.12 (s, 1 H), 6.99 (m, 2 H), 10.12 (bs, 1H). Anal. Calcd. For $C_{31}H_{38}F_3N_4O_5$: C, 61.73; H, 6.18; N, 9.29. Found: C, 61.80; H, 6.24; N, 9.39;

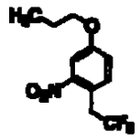
Step 1: 1-Methyl-3-nitro-4-propoxy-benzene



Potassium carbonate (13.5 g; 0.098 mol) followed by 1-iodopropane (9.58 mL, 0.098 mol) were added to a solution of 4-methyl-3-nitro-phenol (15 g, 0.098 mol) in DMF (100mL). The mixture was stirred for 5 hours and then partitioned between H_2O and EtOAc. The organic

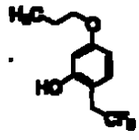
layer was washed with sold $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated to a clear oil (17.5g).

Step 2: 2-Nitro-4-propoxy-1-(2,2,2-trifluoro-ethyl)-benzene



1-Methyl-2-nitro-4-propoxy-benzene (17.0g, 87mmol) was dissolved in CCl_4 (100ml) and NBS (15.59g, 87mmol) followed by benzoyl peroxide (1.0mg 5 mol%) were added. The reaction was heated to reflux and stirred as such for 24hrs, after which time the mixture was cooled to room temperature and filtered. The filtrate was concentrated and purified by flash column chromatography (0% to 5% EtOAc in hexanes) to give the bromide as a white solid (7.0g). Trimethyl(trifluoromethyl)silane (4.8mL, 31.9 mmol) was added to a stirred mixture of the bromide (7.0g, 25.5 mmol), KF (1.85g, 31.90 mmol), CuI (7.28g, 38.25 mmol) in DMF (50 mL) and NMP (50 mL). The reaction mixture was heated to 55 °C under N_2 for 15 hours. The mixture was poured into water, made basic with 1N NaOH and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to a black oil, and purified by flash column chromatography (0% to 10% EtOAc in hexanes) to give the product as a yellow oil (3.0g). ^1H NMR (300MHz, $CDCl_3$): δ 1.06 (t, J=6.79 Hz, 3 H) 1.80 (m, 2 H), 3.68 (q, J=10.47 Hz, 2 H), 3.78 (t, J=6.56 Hz, 2 H) 6.76 (d, J=2.33 Hz, 1 H) 7.33 (d, J=2.33 Hz, 1 H), 7.69 (s, 1 H).

Step 3: 5-Propoxy-2-(2,2,2-trifluoro-ethyl)-phenol

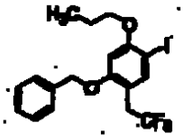


2-Nitro-4-propoxy-1-(2,2,2-trifluoro-ethyl)-benzene(3.0g) was dissolved in ethanol (50ml) and 10% palladium on carbon (1.0g) was added. The mixture was hydrogenated by use of balloon for 6hrs, after which time the catalyst was filtered off through a plug of celite. The filtrate was concentrated and purified by flash column chromatography (0% to 60% EtOAc in hexanes) to give the aniline as a yellow oil (2.5g). This aniline was suspended in H_2SO_4 (2.05ml in 6ml water) and cooled to -5°C. Sodium nitrite (814mg in water 5ml) was added dropwise. The mixture was stirred at 0°C for a further 30 mins and then the mixture was added to a solution of sulfuric acid (19ml in water 100ml). The mixture was heated to 80°C for 1hr. The reaction mixture was cooled to room temperature and the product was extracted using ethyl acetate. The organics were separated and dried over magnesium sulfate and the solvent was

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178

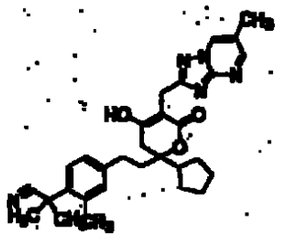
concentrated. The residue was purified flash column chromatography (0% to 50% EtOAc in hexanes) to afford the product as a red solid (500mg). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.08 (t, J=6.79 Hz, 3 H) 1.80 (m, 2 H), 3.46 (q, J=10.33 Hz, 2 H), 3.92 (t, J=6.86 Hz, 2 H) 6.26 (d, J=2.33 Hz, 1 H) 6.48 (s, 1 H) 7.10 (d, J=2.33 Hz, 1 H), 8.40 (bs, 1 H).

Step 4: 1-Benzyloxy-4-iodo-5-propoxy-2-(2,2,2-trifluoro-ethyl)-benzene



The title compound was prepared analogously to example A(75) where 5-propoxy-2-(2,2,2-trifluoro-ethyl)-phenolfrom step 3 above was substituted in place of 2-methyl-5-(2,2,2-trifluoro-ethyl)-phenol in step 4 of that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.08 (t, J=6.79 Hz, 3 H) 1.80 (m, 2 H), 3.46 (q, J=10.56 Hz, 2 H), 4.00 (t, J=6.56 Hz, 2 H) 4.99 (s, 2 H), 6.65 (s, 1 H) 7.26-7.42 (m, 6 H).

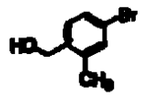
Example A(76): 2-[4-(2-[2-Cyclopentyl-4-hydroxy-6-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-methylphenyl]-2-methylpropanenitrile



6-Methyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde (0.11 g, 0.7 mmol) was added to a solution of 2-[4-[2-(2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)-ethyl]-2-methyl-phenyl]-2-methyl-propionitrile (0.16g, 0.5 mmol, from step 5 below) in MeOH (4 mL). The reaction mixture was stirred for 15 mins and then treated with borane-dimethylamine complex (34 mg, 0.6 mmol). After 15 hours the reaction mixture was filtered through a glass frit washing with MeOH. The filtrate was concentrated to a yellow oil. Purification by prep HPLC gave the product as a white powder (32 mg, 14% yield). ^{1}H NMR (400MHz, DMSO-d_6): 1.35-1.46 (2 H, m) 1.75 (6 H, s) 1.77-1.81 (2 H, m) 1.93-2.04 (3 H, m) 2.35-2.46 (2 H, m) 2.48 (3 H, s) 2.52-2.56 (2 H, m) 2.59 (3 H, s) 2.61 – 2.76 (4 H, m) 4.10 (2 H, d, J=6.06 Hz) 6.96 - 7.02 (2 H, m) 7.15 - 7.23 (1 H, m) 8.57 - 8.63 (1 H, m) 8.69 (1 H, d, J=2.53 Hz). MS (ESI): 512 (M-H).

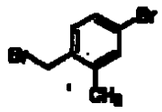
Step 1: (4-Bromo-2-methyl-phenyl)-methanol

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179



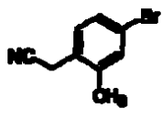
4-Bromo-2-methyl-benzoic acid (9.88 g, 45.9 mmol) was dissolved in THF (100 ml), and the solution was cooled to 0 °C. To this solution, a solution of 1M BH_3·THF (91.89 ml, 91.89 mmol) was added at 0 °C, and the solution was vigorously stirred for 3 hours at room temperature. The reaction mixture was diluted with cold water (20 mL), washed with a saturated solution of $NaHCO_3$, then extracted with ether 3 times (300 mL). The combined organic ether was washed with brine (250 mL), dried over $MgSO_4$, and concentrated in *Vacuo*. The residue was purified via flash column chromatography (25% to 55% EtOAc in Hexane) to give white solid (8.24 g, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (2 H, s) 4.64 (1 H, d, *J*=5.81 Hz) 7.20 - 7.28 (2 H, m) 7.30 - 7.36 (1 H, m).

Step 2: 4-Bromo-1-bromomethyl-2-methyl-benzene



Triphenylphosphine (11.35 g, 43.27 mmol) followed by carbon tetrabromide (14.35 g, 43.27 mmol) were added to a solution of (4-bromo-2-methyl-phenyl)-methanol (7.25 g, 36 mmol) in CH_2Cl_2 (200 mL). The mixture was stirred at room temperature for 5 hours. The solution was concentrated to 15 mL. The residue was purified by flash column chromatography (1% to 10% EtOAc in Hexane) gave the product as brown oil (9.25 g, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.39 (3 H, s) 4.45 (2 H, s) 7.17 (1 H, d, *J*=8.08 Hz) 7.29 (2 H, m) 7.30 (1 H, dd, *J*=8.08, 2.02 Hz) 7.34 (1 H, s).

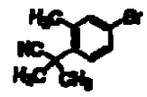
Step 3: (4-Bromo-2-methyl-phenyl)-acetonitrile



To a solution of 4-bromo-1-bromomethyl-2-methyl-benzene (3.96 g, 15 mmol) dissolved in DMF (16 mL) were added sodium cyanide (0.85 g, 17.25 mmol) and water (1.8 mL). The reaction was stirred for overnight at room temperature. To the reaction was added 100 mL water, 80 mL saturated $NaHCO_3$, and 100 mL EtOAc. The layers were separated, and the aqueous layer was extracted with 3 x 100 mL EtOAc. The combined organics were washed with 100 mL water, and then dried over Na_2SO_4. After filtering off the solids, the mother liquor was concentrated to the desired product by rotary evaporation (2.82 g, 92.7% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (2 H, s), 3.62 (1 H, s), 7.20-7.27 (1 H, m), 7.32-7.41 (1 H, m).

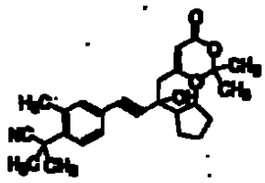
Step 4: 2-(4-Bromo-2-methyl-phenyl)-2-methyl-propionitrile

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180



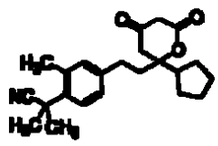
To a solution of (4-bromo-2-methyl-phenyl)-acetonitrile (1.26 g, 6 mmol) from step 3 above in DMF (15 mL) cooled to –10°C was added a potassium t-butoxide (1.62 g, 14.4 mmol). The reaction was stirred for 15 minutes, iodomethane (0.86 mL, 13.8 mmol) was added slowly. The reaction was stirred for 2 hours then quenched with HOAc (0.51 mL, 9 mmol). The reaction mixture stirred for 20 minutes and mixed with IPE (250 mL) and water (200 mL). The layers were separated, and the aqueous layer was extracted with 3 x 100 mL IPE. The combined organics were washed with 200 mL water, and then dried over $MgSO_4$. After filtering off the solids, the mother liquor was concentrated to the crude product by rotary evaporation. The residue was purified by flash column chromatography (0% to 75% EtOAc in Hexane) to give the desired product. Yield: 1.28 g, 89%. ^1H NMR (400 MHz, $CDCl_3$): δ 1.77 (6 H, s) 2.62 (3 H, s) 7.16 (1 H, d, J=8.59 Hz) 7.31 - 7.40 (2 H, m).

Step 5: 2-(4-[2-(3-Cyclopentyl-4-hydroxy-5- (8-methyl-[1,2,4]triazolo[1,5-a]pyridin-8-ylmethyl)-6-oxo-3,6-dihydro-2H-pyran-2-yl]-ethyl]-2-methyl-phenyl)-2-methyl-propionitrile



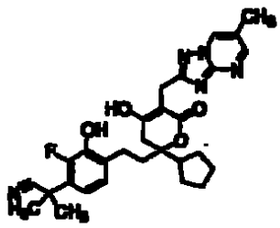
A mixture of 2-(4-bromo-2-methyl-phenyl)-2-methyl-propionitrile (1.24 g, 5.2 mmol), 6-(2-cyclopentyl-2-hydroxybut-3-ynyl)-2,2-dimethyl-4*H*-1, 3-dioxin-4-one (1.37 g, 5.2 mmol), $PdCl_2(PPh_3)_2$ (0.13 g, 4 mol%) and CuI (7.9 mg, 8 mol%). in diisopropylamine (4 mL) and DMF (8 mL) was heated at 80°C for 40 min. The reaction mixture was cooled to room temperature and diluted with EtOAc (250 mL), then washed with aqueous NH_4Cl, brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography to give the desired product. Yield: 1.28 g, 57%. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.38-1.40 (1 H, m) 1.52 - 1.62 (6 H, m) 1.66 - 1.71 (7 H, m) 1.92 - 1.99 (2 H, m) 2.33 - 2.42 (2 H, m) 2.53 (3 H, s) 2.56 - 2.67 (3 H, m) 5.43 (1 H, s) 6.95 - 7.04 (2 H, m) 7.22 (1 H, d, J=8.08 Hz). MS (ESI): 420 (M-H).

Step 6: 6-Cyclopentyl-6-[2-(5-ethyl-4-hydroxy-3-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione



2-(4-[3-Cyclopentyl-4-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-3-hydroxy-but-1-ynyl]-2-methyl-phenyl)-2-methyl-propionitrile (1.23 g, 3.0 mmol, from step 5 above was dissolved in and treated with $Pd(OH)_2$ (0.36 g, 20wt% Degussa type). The mixture was stirred under a balloon of hydrogen overnight. The reaction mixture was filtered through a celite pad, followed by washing with EtOAc. The filtrate was concentrated to a pale yellow solid. The solid was dissolved in NaOH (0.3 M in MeOH, 15 mL, 4.5 mmol). The reaction was stirred at room temperature for 3 hours then quenched with 75 mL saturated NH_4Cl and 3 mL 1 N HCl. To this solution was added 100 mL CH_2Cl_2 and the layers were separated. The aqueous layer was extracted with 2 x 75 mL CH_2Cl_2 and the organic layers were combined. After drying the organic layer with $MgSO_4$, and filtering to remove the solids, the solvent was removed by rotary evaporation. The remaining oil was purified by flash chromatography to yield the desired product (0.52 g, 47% yield). ^1H NMR (400 MHz, $CDCl_3$): δ: 1.38-1.40 (1 H, m) 1.52 - 1.62 (6 H, m) 1.65 - 1.71 (7 H, m) 1.92 - 1.99 (2 H, m) 2.33 - 2.42 (2 H, m) 2.53 (3 H, s) 2.56 - 2.67 (3 H, m) 5.43 (1 H, s) 6.95 - 7.04 (2 H, m) 7.22 (1 H, d, J=8.08 Hz). MS (ESI): 366 (M-H).

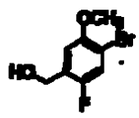
Example A(79): 2-[4-(2-[2-Cyclopentyl-4-hydroxy-5-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-5,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluoro-5-hydroxyphenyl]-2-methylpropanenitrile



2-(4-[2-[1-Cyclopentyl-3-hydroxy-4-(8-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-5-oxo-cyclohex-3-enyl]-ethyl]-2-fluoro-5-methoxy-phenyl)-2-methyl-propionitrile from step 2 below ((168 mg, 0.3 mmol) in CH_2Cl_2 was cooled to -78 °C. 1M boron tribromide (3.06 mL, 3.1 mmol) was slowly added at -78 °C. The reaction mixture was then stirred for 0.5 hr at -78 °C, and at room temperature for an additional 2.5 hrs. Ice water (6 mL), followed by concentrated HCl (0.5 mL), were slowly added to the reaction mixture. The resulting mixture was stirred for another 0.5 hr then extracted 3 times with CH_2Cl_2 (3x75 mL). The combined organic CH_2Cl_2 layer was washed with brine (75 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was

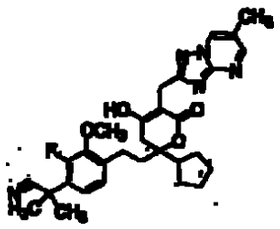
purified via flash column chromatography to give the desired product (25 mg, 15% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.69 - 1.79 (10 H, m) 1.90-1.98 (3 H, m) 2.33-2.48 (2 H, m) 2.45-2.59 (6 H, m) 2.58-2.69 (4 H, m) 4.02-4.16 (2 H, m) 6.76 (1 H, d, J=11.87 Hz) 6.91 (1 H, d, J=6.82 Hz) 6.62 (1 H, s) 6.70 (1 H, s). MS (ESI): 532 (M-H).

Step 1: (4-Bromo-2-fluoro-5-methoxy-phenyl)-methanol



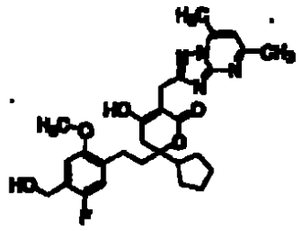
Bromine (15 mL, 0.3 mol) was added slowly to a solution of 2-fluoro-5-methoxy-benzaldehyde (23.1g, 0.15 mol) in chloroform (600 mL) and the mixture was stirred at room temperature for 5 days. The mixture was poured into water (200 ml) and extracted with chloroform (2x 200 mL). The organics were washed with water, brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (2-15% EtOAc in hexanes to give 4-bromo-2-fluoro-methoxy-benzaldehyde (20.7g, 60%). To a solution of 4-bromo-2-fluoro-5-methoxy-benzaldeyde (4.0 g, 17.3 mmol) in MeOH at 0 °C was added $NaBH_4$ (0.65 g, 17.3 mmol). After the reaction mixture was stirred at 0 °C for 2 hours, it was allowed to warm to room temperature. The organic layer was taked up in ethyl ether washed with water and dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (25-45% EtOAc in hexanes) to give the product. (3.9g, 99%). ^{1}H NMR (300MHz, $CDCl_3$): δ 3.90 (s, 3 H), 4.74 (d, J=6.02 Hz, 2 H), 6.82 (q, J=6.1 Hz, 1 H), 7.29 (d, J=10.59 Hz, 1 H).

Step 2: 2-(4-[3-[2-Cyclopentyl-4-hydroxy-8-(8-methyl-[1,2,4]triazolo[1,5-a]pyridin-8-ylmethyl)-6-oxo-6,8-dihydro-2H-pyran-3-yl]-ethyl]-5-fluoro-2-methoxy-phenyl)-2-methyl-propionitrile



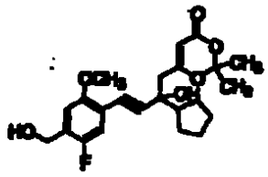
The title compound was prepared analogously to example A(76)where 4-bromo-2-fluoro-5-methoxy-phenyl)-methanol was substituted in place of (4-bromo-2-methyl-phenyl)-methanol in step 1 of that example. MS (ESI): 546 (M-1)

Example A(80): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[5-fluoro-4-(hydroxymethyl)-2-methoxyphenoxy]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



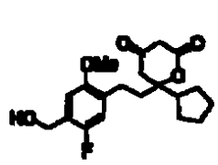
The desired product was prepared analogously to example A(1) substituting 6-cyclopentyl-6-[2-(5-fluoro-4-hydroxymethyl-2-methoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione (364 mg, 1.0 mmol) from step 2 below in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione. Yield: 52 mg, 12%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 - 1.57 (2 H, m) 1.82 – 2.00 (3 H, m) 2.56-2.75 (12 H, m) 2.79 (3 H, s) 3.78 (3 H, s) 4.12 (2 H, s) 4.66 – 4.72 (3 H, m) 6.76 (1 H, d, J=10.11 Hz) 6.81 (1 H, d, J=6.81 Hz) 9.93 (1 H, s). MS (ESI): 523 (M-H).

Step 1: 6-[2-Cyclopentyl-4-(5-fluoro-4-hydroxymethyl-2-methoxy-phenyl)-2-hydroxy-but-3-ynyl]-2,2-dimethyl-[1,3]dioxin-4-one



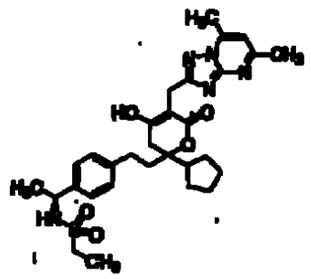
The desired product was prepared analogously to step 5 of example A(79) , substituting (4-bromo-2-fluoro-5-methoxy-phenyl)-methanol (2.35 g, 10.0 mmol) from step 1 of A(79) in place of 2-(4-bromo-2-methyl-phenyl)-2-methyl-propionitrile. Yield: 4.4 g, 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 – 1.45 (1 H, m) 1.52 – 1.64 (3 H, m) 1.65 – 1.79 (9 H, m) 1.79 – 1.85 (2 H, m) 2.18 – 2.27 (1 H, m) 2.37 – 2.49 (1 H, m) 2.53 – 2.66 (3 H, m) 3.62 (3 H, s) 4.73 (2 H, s) 5.53 (1 H, s) 6.91 – 7.01 (2 H, m). MS (ESI): 417 (M-H).

Step 2: 6-Cyclopentyl-6-[2-(5-fluoro-4-hydroxymethyl-2-methoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione



The desired product was prepared analogously to example A(2), where 6-[2-cyclopentyl-4-(5-fluoro-4-hydroxymethyl-2-methoxy-phenyl)-2-hydroxy-but-3-ynyl]-2,2 dimethyl-[1,3]dioxin-4-one (1.28 g, 3.03 mmol) was substituted in place 6-[2-Cyclopentyl-4-(2-ethyl-6-methoxy-pyridin-4-yl)-2-hydroxy-but-3-ynyl]-2,2-dimethyl-[1,3]dioxin-4-one. Yield: 1.4 g, 38%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.37 – 1.49 (1 H, m) 1.53 – 1.97 (9 H, m) 2.53 – 2.6 (1 H, m) 2.64 – 2.7 (1 H, m) 2.75 (2 H, s) 3.41 (2 H, s) 3.79 (3 H, s) 4.71 (2 H, s) 6.79 (1 H, d, J=9.85 HZ) 6.87 (1 H, d, J=5.81 Hz). MS (ESI): 363 (M-H).

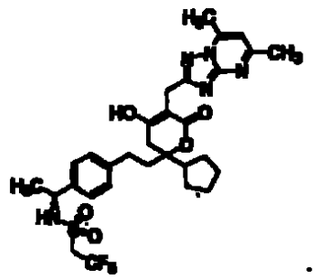
Example A(81): N-[(1R)-1-[4-(2-[2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-6-yl]ethyl)phenyl]ethyl]ethanesulfonamide



The title compound was prepared analogously to example A(1) where N-((1R)-1-(4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]phenyl)ethyl)ethanesulfonamide (Example A(87)was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione of that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.07 (t, J=7.3 Hz, 3 H), 1.4(d, J=6.9 Hz, 3 H), 1.5-1.8 (m, 9 H), 2.11-2.16 (m, 2 H), 2.48-2.59 (m, 7 H), 2.78-2.83 (m, 3 H), 3.71 (d, J=16 Hz, 1 H), 3.85 (d, J=16 Hz, 1 H), 4.08 (t, J=14, 7.3 Hz, 2 H), 4.39-4.45 (m, 1 H), 7.06 (s, 1 H), 7.21-7.31 (m, 4 H), 7.66 (d, J=8.3 Hz, 1 H), 10.9 (s, 1 H). Anal. Calcd. For $C_{29}H_{39}N_3O_8S$: C, 61.94; H, 6.76; N, 12.04. Found: C, 61.80; H, 6.87; N, 12.20. ESIMS (M+1+): 582.

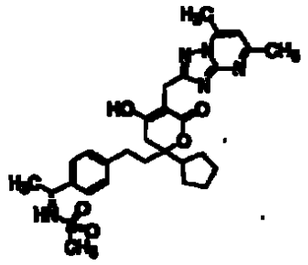
Example A(82): N-[(1R)-1-[4-(2-[2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)phenyl]ethyl]-2,2,2-trifluoroethanesulfonamide

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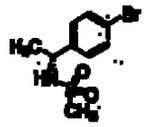
The title compound was prepared analogously to example A(1) where N-((1R)-1-(4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]phenyl)ethyl)-2,2,2-trifluoroethanesulfonamide (Example A(88))was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione of that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.46 (d, J=6.6 Hz, 3 H), 1.55-1.81 (m, 11 H), 2.16-2.20 (m, 2 H), 2.52-2.63 (m, 7 H), 2.81 (d, J=17 Hz, 1 H), 3.77 (d, J=16 Hz, 1 H), 3.9 (d, J=16 Hz, 1 H), 4.22-4.33 (m, 2 H), 4.56-4.63 (m, 1 H), 7.09 (s, 1 H), 7.27-7.34 (m, 4 H), 8.41 (d, J=8.3 Hz, 1 H), 11 (s, 1 H). Anal. Calcd. For $C_{29}H_{36}F_3N_5O_6S$. 0.5 H_2O: C, 55.89; H, 5.75; N, 10.86. Found: C, 55.01; H, 5.80; N, 10.94. ESIMS (M+H+): 638.

Example A(93): N-[(1R)-1-[4-[2-[2-cyclopentyl-5-[[5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]phenyl]ethyl]methanesulfonamide



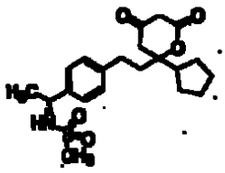
The title compound was prepared analogously to example A(1) where *N*-(1-[4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-phenyl]-ethyl)-methanesulfonamide from step 2 belowwas substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione of that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.4(d, J=6.6 Hz, 3 H), 1.5-1.8 (m, 9 H), 2.10-2.13 (m, 2 H), 2.48-2.64 (m, 10 H), 2.82 (d, J=17 Hz, 1 H), 3.35 (s, 2 H), 3.71-3.86 (m, 2 H), 4.43-4.48 (m, 1 H), 7.08 (s, 1 H), 7.22-7.31 (m, 4 H), 7.84 (d, J=8.3 Hz, 1 H), 10.89 (s, 1 H). Anal. Calcd. For $C_{25}H_{30}N_2O_5S$: C, 61.36; H, 6.57; N, 12.34. Found: C, 61.47; H, 6.80; N, 12.30.

Step 1: (R) *N*-[1-(4-Bromo-phenyl)-ethyl]-methanesulfonamide.



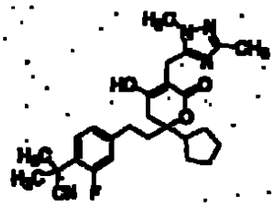
To a stirred solution of (R)-(+)-1-(4-bromophenyl)ethylamine (0.5g, 2.49 mmol), in anhydrous CH_2Cl_2 (5mL) under argon were added methane sulfonyl chloride (0.23 mL, 2.99 mmol) and pyridine (0.30 mL, 3.73 mmol). The resulting solution was stirred at 25 °C for 3 hrs. The reaction mixture was quenched with 1N HCl and extracted with EtOAc (30 mL). The organic phase was washed with brine (50 mL), dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (50% EtOAc in hexanes) to give the product (0.40 g, 58%) as a white solid. ^{1}H NMR ($CDCl_3$) δ: 1.52 (d, J = 6.8 Hz, 3 H), 2.67 (s, 3 H), 4.61-4.72 (m, 2 H), 7.24 (d, J = 8.3 Hz, 2 H), 7.51 (d, J = 8.3 Hz, 2 H). ESIMS (MNa+): 279.

Step 2: *N*-(1-{4-[2-(2-Cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-phenyl}-ethyl)-methanesulfonamide



The title compound was prepared analogously to example A(2) where *N*-[1-(4-bromo-phenyl)-ethyl]-methanesulfonamide from step 1 above was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example. ^{1}H NMR (300 MHz, CDCl3): δ 1.52 (d, J = 7.2 Hz, 3 H), 1.58-1.72 (m, 6 H), 1.93-2.05 (m, 2 H), 2.27-2.30 (m, 2 H), 2.93 (s, 3 H), 2.45-2.46 (m, 1 H), 2.78 (s, 2 H), 3.42 (d, J = 2.7 Hz, 2 H), 4.54 (d, J = 3.0 Hz, 1 H), 4.60-4.65 (m, 1 H), 7.15 (d, J = 8.3 Hz, 2 H), 7.28 (d, J = 8.3 Hz, 2 H). Anal. Calcd. For $C_{21}H_{29}NO_5S$: C, 61.89; H, 7.17, N, 3.44; Found: C, 61.94; H, 7.40, N, 3.69. ESIMS (M-H-): 406.

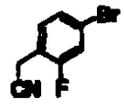
Example A(94): 2-[4-(2-{2-Cyclopentyl-5-[(1,3-dimethyl-1H-1,2,4-triazol-5-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile



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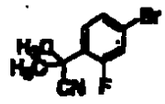
The title compound was prepared analogously to example A(1), where 2-{4-[2-(2-Cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-2-methyl-propionitrile from step 3 below, was substituted in place of 6-[2-(3-Chloro-5-ethyl-4-methoxy-phenyl)-ethyl]-6-cyclopentyl-dihydro-pyran-2,4-dione and 2,5-Dimethyl-2*H*-[1,2,4]triazole-3-carbaldehyde was substituted instead of 5,7-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde in that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.49-1.69 (m, 8 H), 1.72 (s, 6 H), 2.06 (s, 3 H), 2.11 (s, 3 H), 2.12-2.13 (m, 2 H), 2.34-2.42 (m, 1H), 2.55-2.68 (m, 3H), 2.80 (d, *J* = 17 Hz, 1 H), 3.42-3.65 (m, 2 H), 7.06-7.16 (m, 2 H), 7.35-7.40 (m, 1 H). Anal. Calcd. For $C_{27}H_{33}FN_4O_3$·0.25 H_2O: C, 66.85; H, 6.96; N, 11.55. Found: C, 66.86; H, 6.99; N, 11.60. EIMS (M+H+): 481.

Step 1: (4-Bromo-2-fluoro-phenyl)-acetonitrile



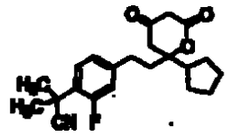
To a solution of 4-bromo-1-bromomethyl-2-fluoro-benzene (8.15 g, 30.4 mmol) dissolved in DMF (16 mL) were added sodium cyanide (2.24 g, 45.6 mmol) and water (2 mL). The reaction was stirred for one hour at 70 °C. To the reaction was added 130 mL water; 120 mL saturated $NaHCO_3$, and 100 mL EtOAc. The layers were separated, and the aqueous layer was extracted with 3 x 100 mL EtOAc. The combined organics were washed with 100 mL water, and then dried over Na_2SO_4. After filtering off the solids, the mother liquor was concentrated to the desired product by rotary evaporation (8.5 g, 99% yield). MS (APCI): 240 (M+H), 242 (M+2+H).

Step 2: 2-(4-Bromo-2-fluoro-phenyl)-2-methyl-propionitrile



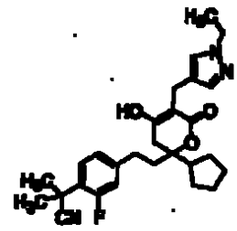
To a slurry of sodium hydride (60% dispersion in mineral oil, 0.82 g, 20.6 mmol) in DMF (20 mL) cooled to 0 °C was added a solution of (4-bromo-2-fluoro-phenyl)-acetonitrile (2.0 g, 9.25 mmol) from Step 1 above, dissolved in THF (10 mL). The reaction was stirred till gas evolution ceased, and then iodomethane (1.3 mL, 20.6 mmol) was added slowly. The reaction was stirred for 30 minutes, and then diluted with 100 mL EtOAc. The solids were removed by filtration, and the organic layer was washed with 100 mL water. The organic layer was dried over $MgSO_4$, and then filtered. The mother liquor was concentrated by rotary evaporation, and the product was distilled under high vacuum (0.3 torr, 45 °C). Yield: 2.25 g, 99%. %. ^{1}H NMR ($CDCl_3$) δ: 2.81 (s, 3H), 2.88 (s, 3H), 7.20 – 7.25 (m, 3H).

Step 3: 2-{4-[2-(2-Cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-2-methyl-propionitrile



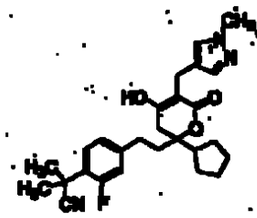
The title compound was prepared analogously to example A(2) where 2-(4-bromo-2-fluoro-phenyl)-2-methyl-propionitrile from step 2 above was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example. ^{1}H NMR ($CDCl_3$) δ: 1.50-1.73(m, 6 H), 1.92-1.98 (m, 2 H), 2.22-2.30 (m, 1 H), 2.65-2.71 (m, 2 H), 2.75-2.80 (m, 2 H), 6.88-6.96 (m, 2 H), 7.37-7.43 (m, 1 H),

Example A(83): 2-[4-(2-{2-Cyclopentyl-6-[(1-ethyl-1H-pyrazol-4-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile



The title compound was prepared analogously to example A(84) where 1-ethyl-1*H*-pyrazole-4-carbaldehyde was substituted instead of 2,5-dimethyl-2*H*-[1,2,4]triazole-3-carbaldehyde in that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.19 (t, J = 7.4 Hz, 3 H), 1.31-1.52 (m, 8 H), 1.70 (s, 6 H), 1.77-1.98 (m, 2 H), 2.55-2.72 (m, 4H), 3.15-3.19 (m, 2H), 3.84 (m, 2 H), 3.99-4.07 (m, 2 H), 6.86-6.91 (m, 2 H), 7.15-7.34 (m, 3 H). Anal. Calcd. For $C_{28}H_{34}FN_3O_5$·0.75 H_2O: C, 66.20; H, 7.25; N, 8.52. Found: C, 67.67; H, 6.99; N, 8.47. ESIMS (MH+): 480.

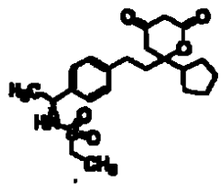
Example A(85): 2-[4-(2-{2-Cyclopentyl-4-hydroxy-6-[(1-methyl-1H-pyrazol-4-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile



The title compound was prepared analogously to example A(84) where 1-methyl-1*H*-pyrazole-4-carbaldehyde was substituted instead of 2,5-dimethyl-2*H*-[1,2,4]triazole-3-carbaldehyde in that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.44-1.82 (m, 8 H), 1.72 (s, 6

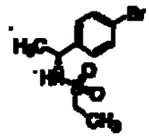
H), 1.88-1.91 (m, 2 H), 2.30-2.36 (m, 2 H), 2.54-2.62 (m, 3 H), 2.72 (d, J = 17 Hz, 1 H), 3.29-3.30 (m, 2 H), 3.73 (s, 3H), 6.89-7.17 (m, 4 H), 7.33-7.45 (m, 1 H). Anal. Calcd. For $C_{27}H_{32}FN_3O_3$·1.0 H_2O: C, 67.06; H, 7.09; N, 8.69. Found: C, 67.20; H, 6.78; N, 8.65. ESIMS (MH+): 466.

Example A(87): N-[(1R)-1-[4-[3-(2-cyclopentyl-4,5-dioxotetrahydro-6H-pyran-6-yl)ethyl]phenyl]ethyl]ethanesulfonamide



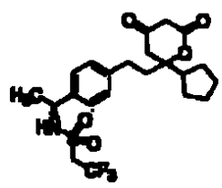
The title compound was prepared analogously to example A(2) where (R)-ethanesulfonic acid [1-(4-bromo-phenyl)-ethyl]-amide from step 1 below was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example. ^{1}H NMR (300 MHz, CDCl3): □ 1.22 (t, J = 7.5 Hz, 3 H), 1.53 (d, J = 6.9 Hz, 3 H), 1.54-1.6 (m, 8 H), 1.93-2.05 (m, 2 H), 2.27-2.30 (m, 2 H), 2.46-2.48 (m, 1 H), 2.65-2.72 (m, 4 H), 2.77 (s, 2 H), 2.83 (d, J = 17 Hz, 1 H), 4.57-4.64 (m, 1 H), 7.13-7.15 (m, 2 H), 7.24-7.28 (m, 2 H). ESIMS (MH+): 420.

Step 1: (R)-Ethanesulfonic acid [1-(4-bromo-phenyl)-ethyl]-amide.



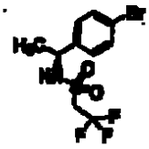
To a stirred solution of (R)-(+)-1-(4-bromophenyl)ethylamine (1g, 5 mmol), in anhydrous CH_2Cl_2 (10mL) under argon were added ethane sulfonyl chloride (0.57 mL, 5.99 mmol) and Pyridine (0.60 mL, 7.5 mmol). The resulting solution was stirred at 25 °C for 3 hrs. The reaction mixture was quenched with 1N HCl and extracted with EtOAc (2x10 mL). The organic phase was washed with brine (50 mL), dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (30% EtOAc in hexanes) to give the product (0.40 g, 56%) as a white solid. ^{1}H NMR ($CDCl_3$) δ: 1.29 (t, J = 7.5 Hz, 3 H), 1.52 (d, J = 6.9 Hz, 3 H), 2.77 (q, J = 14, 7.5 Hz, 2 H), 4.61-4.72 (m, 2 H), 7.24 (d, J = 8.3 Hz, 2 H), 7.51 (d, J = 8.3 Hz, 2 H). ESIMS (MH+): 293.

Example A(88): N-[(1R)-1-[4-[3-(2-cyclopentyl-4,5-dioxotetrahydro-6H-pyran-6-yl)ethyl]phenyl]ethyl]-2,2,2-trifluoroethanesulfonamide



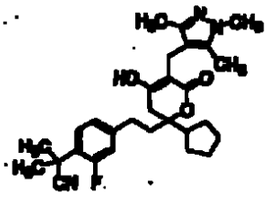
The title compound was prepared analogously to example A(1) where (R) 2,2,2-trifluoro-ethanesulfonic acid [1-(4-bromo-phenyl)-ethyl]-amide, from step 1 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (300 MHz, CDCl3): δ 1.17-1.21 (m, 3 H), 1.51-1.8 (m, 8 H), 1.93-2.0 (m, 2 H), 2.27-2.30 (m, 2 H), 2.67-2.70 (m, 2 H), 2.77 (s, 2 H), 3.71-3.74 (m, 2 H), 3.80-3.83 (m, 1 H), 4.68-4.72 (m, 1 H), 7.16-7.29 (m, 5 H). ESIMS (MH+): 474.

Step 1: (R)-2,2,2-Trifluoro-ethanesulfonic acid [1-(4-bromo-phenyl)-ethyl]-amide.



The title compound was prepared analogously to step 1 from example A(81) where 2,2,2'-trifluoroethanesulfonyl chloride was substituted in place of ethane sulfonyl chloride of that example. ^{1}H NMR ($CDCl_3$) δ: 1.53 (d, J = 6.8 Hz, 3 H), 2.70-2.9 (m, 2 H), 4.61-4.72 (m, 2 H), 7.24 (d, J = 8.3 Hz, 2 H), 7.51 (d, J = 8.3 Hz, 2 H). ESIMS (MH+): 345

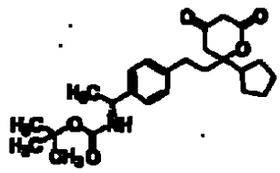
Example A(85): 2-[4-(2-{2-Cyclopentyl-4-hydroxy-6-oxo-5-[(1,3,5-trimethyl-1H-pyrazol-4-yl)methyl]-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile



The title compound was prepared analogously to example A(84) where 1,3,5-trimethyl-1*H*-pyrazole-4-carbaldehyde was substituted instead of 2,5-dimethyl-2*H*-[1,2,4]triazole-3-carbaldehyde in that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.45-1.69 (m, 8 H), 1.72 (s, 6 H), 1.82-1.88 (m, 2 H), 2.09 (s, 3 H), 2.12 (s, 3 H), 2.26-2.31 (m, 1 H), 2.49-2.58 (m, 3 H), 2.71 (d, J = 17 Hz, 1 H), 3.12 (d, J = 14 Hz, 1 H), 3.24 (d, J = 14 Hz, 1 H), 3.54 (s, 3 H), 6.94 (dd, J =8.4, 1.8 Hz, 1 H), 7.04 (dd, J = 13, 1.8 Hz, 1 H), 7.26 (t, J =8.4Hz 1 H), 10.68 (s, 1 H). Anal. Calcd. For $C_{28}H_{36}FN_3O_3$: C, 70.56; H, 7.35; N, 8.51. Found: C, 70.70; H, 7.45; N, 8.50. ESIMS (MH+): 494.

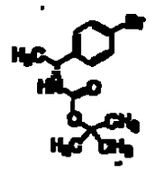
190
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Example A(90): tert-Butyl (1R)-1-{4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-3-yl)ethyl]phenyl}ethylcarbamate



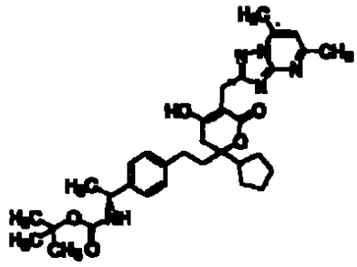
The title compound was prepared analogously to example A(2) where (R)-[1-(4-bromo-phenyl)-ethyl]-carbamic acid tert-butyl ester from step 1 below was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.18 (d, J = 6.6 Hz, 3 H), 1.35-1.69 (m, 17 H), 1.94-1.98 (m, 2H), 2.27-2.31 (m, 1 H), 2.63-2.69 (m, 2 H), 2.77 (s, 2 H), 3.42 (s, 2 H), 3.81-3.86 (m, 1 H), 4.76 (bm, 1 H), 7.10 (d, J = 8.1 Hz, 2 H), 7.23 (d, J = 8.1 Hz, 2 H). ESIMS (M+H+): 430.

Step 1: (R)-[1-(4-Bromo-phenyl)-ethyl]-carbamic acid tert-butyl ester.



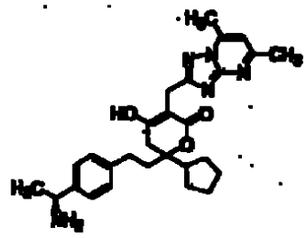
To a stirred solution of (R)-(+)-1-(4-bromophenyl)ethylamine (5g, 24.99 mmol), in dioxane (50mL) under argon were added di-tert-butyl dicarbonate (6 g, 27.5 mmol) and NaOH 0.5 M (50 mL). The resulting solution was stirred at 25 °C overnight. The reaction mixture was partitioned between ethyl acetate and 10% citric acid and extracted with ethyl acetate (3x100 mL). The organic phase was washed with brine (50 mL), dried over Na_2SO_4 and evaporated. The residue solidified to a white solid and was used without further purification. (7 g, 99%). ^{1}H NMR ($CDCl_3$) δ 1.32-1.34 (m, 12 H), 4.66-4.71 (m, 2 H), 7.29-7.12 (m, 2H), 7.36-7.39 (m, 2H). ESIMS (M+H+): 302.

Example A(91): tert-Butyl (1R)-1-{4-(2-[2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-5,6-dihydro-2H-pyran-3-yl]ethyl}phenyl)ethylcarbamate



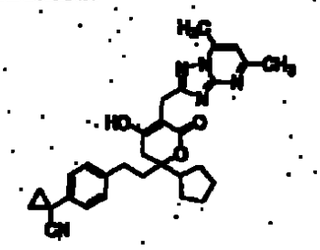
The title compound was prepared analogously to example A(1) where *tert*-butyl (1R)-1-{4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]phenyl}ethylcarbamate (Example A(90) was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione of that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.24-1.88 (m, 21 H), 2.06-2.08 (m, 2H), 2.42-2.61 (m, 9 H), 2.77 (d, *J* = 16 Hz, 1 H), 3.73 (d, *J* = 16 Hz, 1 H), 3.82 (d, *J* = 16 Hz, 1 H), 4.33-4.55 (m, 1 H), 7.05-7.08 (m, 1 H), 7.29-7.40 (m, 4 H), 8.35 (s, 1 H), 11 (s, 1 H). ESIMS (M+H+): 520.

Example A(92): 6-(2-{4-[(1R)-1-Aminoethyl]phenyl}ethyl)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



To a stirred solution of *tert*-butyl (1R)-1-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)phenyl]ethylcarbamate (0.58g, 0.86 mmol, example A(91)) in dioxane (2 mL) under argon was added 4 N HCl in dioxane (2 mL). The resulting solution was stirred at 25 °C for 30 minutes. The solvents were completely evaporated and the resultant white solid was recrystallized from ethyl acetate to give the product (0.40 g, 80%) as a white solid. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.56-1.77 (m, 11 H), 2.14-2.18 (m, 2H), 2.57-2.86 (m, 10 H), 3.77-3.94 (m, 2 H), 4.40-4.43 (m, 1 H), 6.6 (bra, 2 H), 7.21 (s, 1 H), 7.38 (d, *J* = 7.9 Hz, 2 H), 7.46 (d, *J* = 7.9 Hz, 2 H), 8.56 (s, 1 H), 11.2 (s, 1 H). Anal. Calcd. For $C_{32}H_{39}N_5O_5$, 1.0 HCl.1.0 H2O: C, 63.74; H, 7.22; N, 13.27. Found: C, 63.60; H, 7.46; N, 13.20. ESIMS (M+H+): 527.

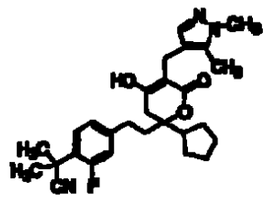
Example A(93): 1-[4-(2-{2-Cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)phenyl]cyclopropanecarbonitrile



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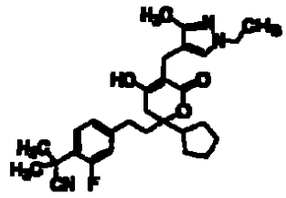
The title compound was prepared analogously to example A(1) where 1-(4-bromophenyl)cyclopropanecarbonitrile was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (400MHz, DMSO-d_6): δ 1.44 – 1.46 (m, 2 H), 1.5-1.7 (m, 8H), 1.73-1.77 (m, 2 H), 2.10-2.15 (m, 2H), 2.50-2.60 (m,11H), 2.82(d, *J* = 16 Hz, 1H), 3.73 (d, *J* = 16 Hz, 1H), 3.85 (d, *J* = 16 Hz, 1H), 7.06 (s, 1H), 7.23-7.32 (m, 4H), 10.87 (s, 1H). ESIMS (M+H+): 512.

Example A(94): 2-[4-(2-[2-Cyclopentyl-5-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile



The title compound was prepared analogously to example A(84) where 1,5-dimethyl-1*H*-pyrazole-4-carbaldehyde was substituted instead of 2,5-dimethyl-2*H*-[1,2,4]triazole-3-carbaldehyde in that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.47-1.66 (m, 8 H), 1.72 (s, 6 H), 1.82-1.89 (m, 2 H), 2.11 (s, 3 H), 2.19 (s, 3 H), 2.29-2.32 (m, 1 H), 2.49-2.56 (m, 3 H), 2.70 (d, *J* = 16 Hz, 1 H), 3.16-3.26 (m, 2 H), 6.96-7.09 (m, 3 H). 7.33-7.39 (m, 1 H), 10.7 (s, 1 H). Anal. Calcd. For $C_{29}H_{34}FN_3O_4$ 0.5 H_2O: C, 68.83; H, 7.22; N, 8.30. Found: C, 68.96; H, 7.23; N, 8.60. ESIMS (M+H+): 492.

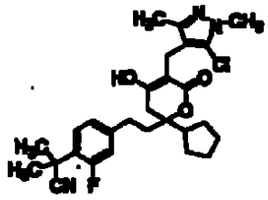
Example A(95): 2-[4-(2-[2-Cyclopentyl-5-[(1-ethyl-3-methyl-1H-pyrazol-4-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile



The title compound was prepared analogously to example A(84) where 1-ethyl-3-methyl-1*H*-pyrazole-4-carbaldehyde was substituted instead of 2,5-dimethyl-2*H*-[1,2,4]triazole-3-carbaldehyde in that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.22 (t, *J* = 7.2 Hz, 3 H), 1.45-1.67 (m, 8 H), 1.72 (s, 6 H), 1.86-1.93 (m, 2H), 2.10 (s, 3 H), 2.19-2.31 (m, 1 H), 2.53-2.61 (m, 2 H), 2.72 (d, *J* = 16 Hz, 1 H), 3.17 (d, *J* = 17 Hz, 1 H), 3.25 (d, *J* = 17 Hz, 1 H), 3.90 (q, *J* = 14, 7.2 Hz, 2 H), 6.99-7.01 (m, 1 H), 7.03 (dd, *J* = 8, 1.8 Hz, 1 H), 7.10 (dd, *J* = 13, 1.8 Hz, 1 H), 7.16 (s, 1 H), 7.36 (t, *J* = 8 Hz, 1 H), 10.8 (s, 1 H). Anal. Calcd. For $C_{30}H_{36}FN_3O_4$ 0.5 H_2O: C, 69.30; H, 7.42; N, 8.38. Found: C, 69.36; H, 7.43; N, 8.39. ESIMS (M+H+): 494.

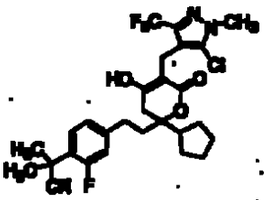
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Example A(96): 2-[4-(2-[5-[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile



The title compound was prepared analogously to example A(84) where 5-chloro-1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde was substituted instead of 2,5-dimethyl-2*H*-[1,2,4]triazole-3-carbaldehyde in that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.42-1.67 (m, 8 H), 1.73 (s, 6 H), 1.88-1.93 (m, 2 H), 2.08 (s, 3 H), 2.11 (s, 3 H), 2.29-2.31 (m, 1 H), 2.51-2.61 (m, 3 H), 2.70 (d, *J* = 17 Hz, 1 H), 3.20 (d, *J* = 14 Hz, 1 H), 3.28 (d, *J* = 14 Hz, 1 H), 7.00 (dd, *J* = 8.2, 1.7 Hz, 1 H), 7.08 (dd, *J* = 13, 1.7 Hz, 1 H), 7.38 (t, *J* =8.2 Hz 1 H), 10.8 (s, 1 H). Anal. Calcd. For $C_{29}H_{35}FClN_3O_3$. 0.25 H_2O: C, 64.88; H, 6.51; N, 8.10. Found: C, 64.73; H, 6.42; N, 8.08. ESIMS (MH+): 516.

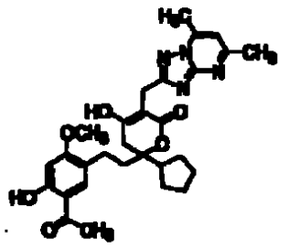
Example A(97): 2-(4-[2-(5-[(5-Chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]methyl)-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl)-2-methylpropanenitrile



The title compound was prepared analogously to example A(84) where 5-chloro-1-methyl-3-trifluoromethyl-1*H*-pyrazole-4-carbaldehyde was substituted instead of 2,5-dimethyl-2*H*-[1,2,4]triazole-3-carbaldehyde in that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.48-1.67 (m, 8 H), 1.76 (s, 6 H), 1.95-1.98 (m, 2 H), 2.38-2.40 (s, 1 H), 2.56-2.72 (m, 4 H), 3.39-3.48 (m, 2 H), 3.86 (s, 3 H), 7.06-7.16 (m, 2 H), 7.37-7.43 (m, 1 H), 11 (s, 1 H). Anal. Calcd. For $C_{29}H_{32}F_4ClN_3O_3$: C, 59.21; H, 5.48; N, 7.40. Found: C, 59.04; H, 5.31; N, 7.32. ESIMS (MH+): 569.

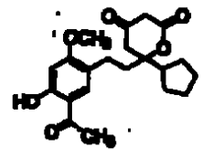
Example A(98): 6-[2-(5-Acetyl-4-hydroxy-2-methoxyphenyl)ethyl]-6-cyclopentyl-3-[(3,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one

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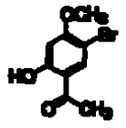
The title compound was prepared analogously to example A(1) where 6-[2-(5-acetyl-4-hydroxy-2-methoxyphenyl)ethyl]-6-cyclopentyldihydro-2H-pyran-2,4(3H)-dione (Example A(99)was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione of that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.34-1.88 (m, 8 H), 1.8-2.08 (m, 3 H), 2.32-2.49 (m, 12 H), 2.85 (d, J=17 Hz, 1 H), 3.57-3.72 (m, 6 H), 6.31 (s, 1 H), 6.90 (s, 1 H), 7.46 (s, 1 H), 12.52 (s, 1 H). Anal. Calcd. For $C_{28}H_{34}N_4O_8$. 0.25 H_2O: C, 64.81; H, 6.45; N, 10.39. Found: C, 64.57; H, 6.39; N, 10.22. ESMS (M+H+): 535.

Example A(99): 6-[2-(5-Acetyl-4-hydroxy-2-methoxyphenyl)ethyl]-6-cyclopentyldihydro-2H-pyran-2,4(3H)-dione



The title compound was prepared analogously to example A(2) where 1-(5-bromo-2-hydroxy-4-methoxy-phenyl)-ethanone from step 1 below was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.51-1.54 (m, 6H), 1.80-1.95 (m, 2H), 2.29-2.39 (m, 1H), 2.57 (s, 3H), 2.57-2.67 (m, 2H), 2.75 (s, 2H), 3.41 (s, 2H), 3.74 (s, 3H), 6.45 (s, 1H), 7.87 (s, 1H), 12.60 (s, 1H). ESMS (M+H+): 374.

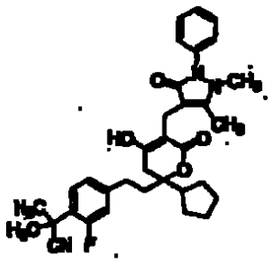
Step 1: 1-(5-Bromo-2-hydroxy-4-methoxy-phenyl)-ethanone.



The title compound was prepared analogously to step 3 from example A(22) where 2'-hydroxy-4'-methoxyacetophenone was substituted in place of 5-ethoxy-2-ethyl-phenol of that example. ^{1}H NMR (300MHz, CDCl3): δ 2.56 (s, 3H), 3.93 (s, 3H), 6.46 (s, 1H), 7.87 (s, 1H), 12.57 (s, 1H). ESMS (M+H+): 244.

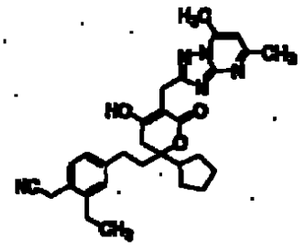
Example A(100): 2-[4-(2-{5-Cyclopentyl-5-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile

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The title compound was prepared analogously to example A(84) where 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde was substituted instead of 2,5-dimethyl-2*H*-[1,2,4]triazole-3-carbaldehyde in that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.45-1.67 (m, 8 H), 1.71 (s, 6 H), 1.88-1.94 (m, 2 H), 2.27-2.30 (m, 1 H), 2.37 (s, 3 H), 2.53-2.65 (m, 4 H), 3.12 (s, 3 H), 3.13-3.18 (m, 2 H), 7.05-7.17 (m,2 H), 7.34-7.41 (m, 5 H), 7.51-7.58 (m, 1 H), 12.3 (s, 1 H). ESIMS (M+H+): 572.

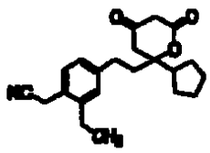
Example A(101): [4-(2-[2-Cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-5,6-dihydro-2H-pyran-3-yl]ethyl)-2-ethylphenyl]acetonitrile



To a solution of [4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-3-yl)ethyl]-2-ethylphenyl]acetonitrile (200mg, 0.57 mmol, example A(102)) in anhydrous MeOH (6 mL) at room temperature was added 5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde (120 mg, 0.68 mmol). The mixture was stirred for 5 min before borane-dimethylamine complex (37 mg, 0.62 mmol) was added. The reaction was stirred at that temperature for 15 hours before it was quenched by the addition of 1.0 N HCl. The solvent was removed and the residue was purified by HPLC to obtain the desired product (80 mg, 21% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.03 (t, J=7.5 Hz, 3 H), 1.32-1.64 (m, 8 H), 2.08 (m, 2 H), 2.36-2.55 (m, 12 H), 2.73 (d, J=17.9 Hz, 1 H), 3.64 (d, J=16.1 Hz, 1 H), 3.77 (d, J=16.4 Hz, 1 H), 3.89 (s, 2 H), 6.95 (s, 1 H), 7.00 (s, 1 H), 7.04 (d, J=7.7 Hz, 1 H), 7.17 (d, J=7.7 Hz, 1 H), 10.81 (s, 1 H).

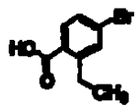
Example A(102): [4-[2-(2-Cyclopentyl-4,6-dioxotetrahydro-2H-pyran-3-yl)ethyl]-2-ethylphenyl]acetonitrile

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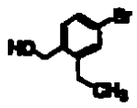
The title compound was prepared analogously to example A(2), where (4-bromo-2-ethyl-phenyl)-acetonitrile (step 4 below) was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine (step 6). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J=7.5 Hz, 3 H), 1.41-1.83 (m, 6H), 1.97 (m, 2 H), 2.27 (m, 1 H), 2.65 (m, 4 H), 2.78 (s, 2 H), 3.43 (s, 2 H), 3.67 (s, 2 H), 7.01 (m, 2 H), 7.29 (d, J=8.3 Hz, 1 H).

Step 1: 4-Bromo-2-ethyl-benzoic acid (4841-146)



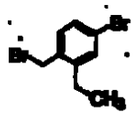
The title compound was prepared according to literature procedure. *J. Med. Chem.*, 1997, 40, 2017-2034.

Step 2: (4-Bromo-2-ethyl-phenyl)-methanol



To a solution of 4-bromo-2-ethyl-benzoic acid (115 mmol) in anhydrous THF (380 mL) at 0°C was added BH_3.THF complex (1.0 N solution in THF, 230 mL) over 30 min. The resulting mixture was slowly warmed up to room temperature and the stirred for 15 hours. The reaction was carefully quenched with slow addition of water. The solvent was removed and the residue was taken up in EtOAc. The organic layer was washed with 1.0 N HCl, H_2O, brine and dried over $MgSO_4$. The solvent was removed to afford the desired product. (22 g, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, J=7.5 Hz, 3 H), 2.64-3.01 (m, 2H), 4.69 (s, 2H), 7.24-7.28 (m, 1H), 7.32-7.36 (m, 2H).

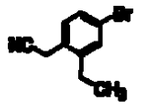
Step 3: 4-Bromo-1-bromomethyl-2-ethyl-benzene



To a solution of (4-bromo-2-ethyl-phenyl)-methanol (7.9 g, 36.7 mmol) in anhydrous $CHCl_3$ (122 mL) was added PBr_3(4.2 mL, 44.1 mmol). The resulting mixture was stirred at room temperature for 2 hours before it was quenched by the addition of water. The organic layer was washed with $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was removed in *vacuo* and the residue was filtered through a pad of silica gel with 20% EtOAc in hexanes. The solvent was

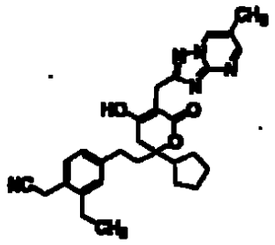
removed in *vacuo* to afford the desired product (8.4 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, J=7.5 Hz, 3 H), 2.71-2.76 (m, 2 H), 4.46 (s, 2H), 7.17-7.20 (m, 1H), 7.29-7.32 (m, 1 H), 7.38-7.39 (m, 1H).

Step 4: (4-Bromo-2-ethyl-phenyl)-acetonitrile



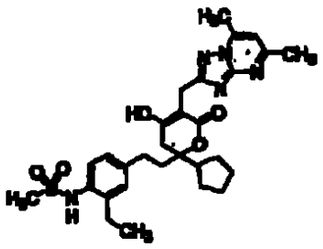
To a solution of 4-bromo-1-bromomethyl-2-ethyl-benzene (2.0 g, 7.25 mmol) in DMF/H_2O (30mL/6 mL) was added potassium cyanide (471 mg, 7.25 mmol). The reaction mixture was heated to 45 °C for 3 hours before it was cooled to room temperature. The mixture was diluted with Et_2O and washed with H_2O, brine and dried over $MgSO_4$. The solvent was removed in *vacuo* to obtain the desired product (1.33g, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, J=7.5 Hz, 3 H), 2.60-2.67 (m, 2 H), 3.68 (s, 2H), 7.23-7.26 (m, 1H), 7.35-7.38 (m, 1 H), 7.38-7.40 (m, 1H).

Example A(103): [4-(2-[2-cyclopentyl-4-hydroxy-6-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenyl]acetonitrile



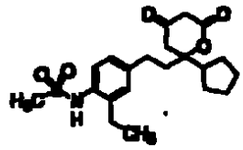
The title compound was prepared analogously to example A(101), where 6-methyl[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde was substituted in place of 5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.15 (t, J=7.5 Hz, 3 H), 1.36-1.71 (m, 8 H), 2.11 (m, 2 H), 2.36 (s, 3 H), 2.42-2.66 (m, 6 H), 2.82 (d, J=16.2 Hz, 1 H), 3.76 (d, J=16.2 Hz, 1 H), 3.84 (d, J=16.1 Hz, 1 H), 3.93 (s, 2 H), 7.11 (m, 2 H), 7.27 (d, J=8.3 Hz, 1 H), 8.71 (s, 1 H), 8.96 (s, 1 H), 10.58 (s, 1 H).

Example A(104): N-[4-(2-[2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenyl]methanesulfonamide



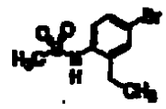
The title compound was prepared analogously to example A(101) where N-(4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-ethyl-phenyl)-methanesulfonamide was substituted in place of (4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-ethylphenyl)acetonitrile. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, J=7.5 Hz, 3 H), 1.41-1.74 (m, 8 H), 2.13 (m, 2 H), 2.47 (s, 3 H), 2.51-2.70 (m, 9 H), 2.83 (d, J=17.7 Hz, 1 H), 2.96 (s, 3 H), 3.74 (d, J=16.4 Hz, 1 H), 3.85 (d, J=16.2 Hz, 1 H), 7.04 (s, 1 H), 7.11 (m, 2 H), 7.20 (d, J=8.6 Hz, 1 H), 8.94 (s, 1 H), 10.86 (s, 1 H).

Example A(166): N-[4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-ethylphenyl]ethanesulfonamide



The title compound was prepared analogously to example A(2), where *N*-(4-bromo-2-ethyl-phenyl)-methanesulfonamide was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine (step 6). ^{1}H NMR (300 MHz, DMSO): δ 1.07 (t, J=7.5 Hz, 3 H), 1.46-1.70 (m, 8H), 1.89-1.95 (m, 2 H), 2.27-2.38 (m, 1 H), 2.56-2.75 (m, 4 H), 2.96 (s, 3 H), 3.42-3.49 (m, 4 H), 4.99 (s, 1H), 7.00-7.03 (m, 1 H), 7.09-7.11 (m, 1 H), 7.17-7.19 (m, 1 H). MS (ESI) (M+Na$^+$): calcd for $C_{21}H_{29}NO_5S$: 430, found 430.

Step 1: *N*-(4-Bromo-2-ethyl-phenyl)-methanesulfonamide

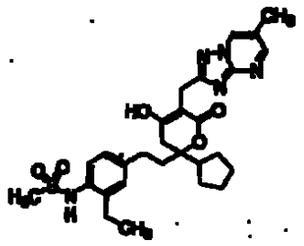


4-Bromo-2-ethyl-aniline (2mL, 14 mmol) dissolved in anhydrous pyridine (35 mL) at room temperature was treated with methylsulfonyl chloride (1.3 mL, 16.8 mmol). The reaction was stirred at that temperature for 15 hours before it was diluted with EtOAc. The mixture was washed with H_2O, brine and dried over $MgSO_4$. The solvent was removed in *vacuo* and the residue was purified with flash chromatography (SiO_2, 5-30% EtOAc in hexanes) to afford the

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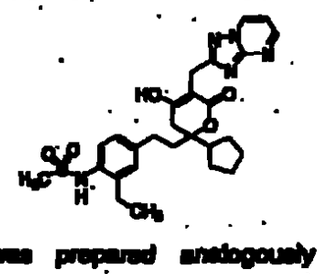
desired product (3.1 g, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J=7.5 Hz, 3 H), 2.61-2.88 (m, 2 H), 3.02 (s, 3 H), 6.35 (s, 1 H), 7.36-7.39 (m, 3 H).

Example A(106): N-[4-(3-(3-cyclopentyl-4-hydroxy-6-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-6-yl)ethyl)-2-ethylphenyl]methanesulfonamide



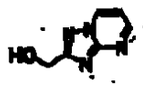
The title compound was prepared analogously to example A(104), where 8-methyl[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde was substituted in place of 5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.93 (t, J=7.3 Hz, 3 H), 1.19-1.54 (m, 8 H), 1.88 (m, 2 H), 2.18 (s, 3 H), 2.28-2.55 (m, 6 H), 2.82 (d, J=17.0 Hz, 1 H), 2.79 (s, 3 H), 3.58 (d, J=15.8 Hz, 1 H), 3.85 (d, J=16.1 Hz, 1 H), 6.90 (d, J=7.54 Hz, 1 H), 6.93 (s, 1 H), 7.01 (d, J=7.9 Hz, 1 H), 8.51 (d, J=6.4 Hz, 1 H), 8.75 (s, 1 H), 8.79 (s, 1 H), 10.69 (s, 1 H).

Example A(107): N-(4-(2-[3-cyclopentyl-4-hydroxy-6-oxo-6-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-3-yl]ethyl)-2-ethylphenyl)methanesulfonamide



The title compound was prepared analogously to example A(104) where [1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde from step 2 below was substituted in place of 5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.06 (t, J=7.2 Hz, 3 H), 1.27-1.71 (m, 8 H), 2.11 (m 2 H), 2.46-2.76 (m, 8 H), 2.83 (d, J=17.1 Hz, 1 H), 2.99 (s, 3 H), 3.78 (d, J=15.8 Hz, 1 H), 3.87 (d, J=16.2 Hz, 1 H), 7.09 (d, J=8.2 Hz, 1 H), 7.13 (s, 1 H), 7.21 (d, J=8.3 Hz, 1 H), 7.27 (dd, J=8.6, 4.3 Hz, 1 H), 8.81 (d, J=4.3, 1.9 Hz, 1 H), 8.95 (s, 1 H), 9.07 (dd, J=8.8, 1.9 Hz, 1 H), 10.9 (s, 1 H).

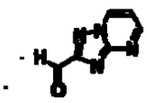
Step 1: [1,2,4]Triazolo[1,5-a]pyrimidin-2-ylmethanol



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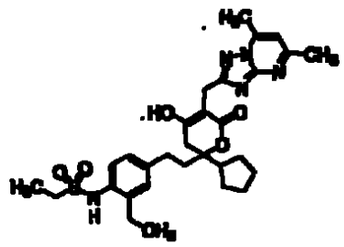
The title compound was prepared analogously to step 7 of example A(1) where malonaldehyde bis(dimethylacetal) was substituted in place of 2,4-pentanedione.

Step 2: [1,2,4]Triazolo[1,5-a]pyrimidine-2-carbaldehyde



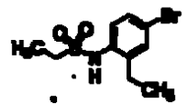
The title compound was prepared analogously to step 8 of example A(1) where [1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethanol was substituted in place of 5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-methanol.

Example A(105): N-[4-(3-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-5,6-dihydro-2H-pyran-3-yl]ethyl)-3-ethylphenyl]ethanesulfonamide



The title compound was prepared analogously to example A(104) where ethanesulfonic acid (4-bromo-2-ethyl-phenyl)-amide was substituted in place of methanesulfonic acid (4-bromo-2-ethyl-phenyl)-amide. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.02 (t, J=7.5 Hz, 3 H), 1.05 (t, J=7.5 Hz, 3 H), 1.29-1.67 (m, 9H), 2.02-2.09 (m, 2 H), 2.39 (s, 3 H), 2.48 (s, 3 H), 2.51-2.56 (m, 2 H), 2.57-2.64 (m, 2 H), 2.71-2.77 (m, 1 H), 2.95-3.02 (m, 2 H), 3.62-3.80 (m, 4 H), 6.95-6.98 (m, 1 H), 7.00-7.04 (m, 2 H), 7.06-7.09 (m, 1 H).

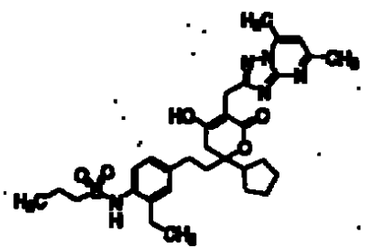
Step 1: Ethanesulfonic acid (4-bromo-2-ethyl-phenyl)-amide



The title compound was prepared analogously to step 1 of example A(105) , where ethylsulfonyl chloride was substituted in place of methylsulfonyl chloride. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J=8.0 Hz, 3 H), 1.39 (t, J=8.0 Hz, 3 H), 2.60-2.66 (m, 2 H), 3.12-3.18 (m, 2 H), 7.32-7.37 (m, 3 H).

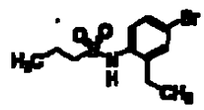
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Example A(109): N-[4-(3-[2-cyclopentyl-5-[[5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenyl]propane-1-sulfonamide



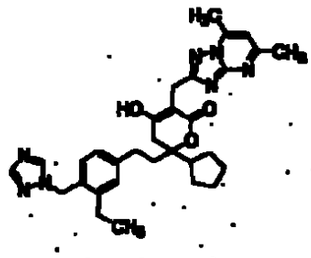
The title compound was prepared analogously to example A(104), where propanesulfonic acid (4-bromo-2-ethyl-phenyl)-amide was substituted in place of methanesulfonic acid (4-bromo-2-ethyl-phenyl)-amide. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.00 (t, *J*=7.5 Hz, 3 H), 1.11 (t, *J*=7.5 Hz, 3 H), 1.55-1.81 (m, 11 H), 2.11-2.17 (m, 2 H), 2.47 (s, 3 H), 2.57 (s, 3 H), 2.62-2.72 (m, 6 H), 3.02-3.07 (m, 2 H), 3.71-3.88 (m, 2 H), 7.04 (s, 1 H), 7.10-7.18 (m, 3 H).

Step 1: Propane-1-sulfonic acid (4-bromo-2-ethyl-phenyl)-amide



The title compound was prepared analogously to step 1 of example A(105) , where propane-1-sulfonyl chloride was substituted in place of methylsulfonyl chloride. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (t, *J*=8.0 Hz, 3 H), 1.25 (t, *J*=8.0 Hz, 3 H), 1.81-1.91 (m, 2 H), 2.80-2.86 (m, 2 H), 3.07-3.10 (m, 2 H), 6.29 (s, 1 H), 7.22-7.37 (m, 3 H).

Example A(110): 6-Cyclopentyl-3-[[5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]methyl]-5-(2-[3-ethyl-4-(1H-1,2,4-triazol-1-ylmethyl)phenyl]ethyl)-4-hydroxy-5,6-dihydro-2H-pyran-2-one

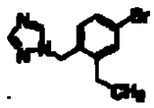


The title compound was prepared analogously to example A(101) where 1-(4-bromo-2-ethyl-benzyl)-1*H*-[1,2,4]triazole was substituted in place of (4-[2-(2-cyclopentyl-4,6-dioxo-

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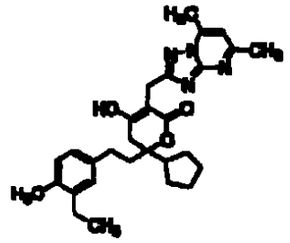
tetrahydro-pyran-2-yl)-ethyl]-2-ethyl-phenyl)-acetonitrile. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.95 (t, J=7.5 Hz, 3 H), 1.31-1.82 (m, 8 H), 2.03 (m 2 H), 2.31 (s, 3 H), 2.35-2.62 (m, 9 H), 2.74 (d, J=19.8 Hz, 1 H), 3.64 (d, J=16.6 Hz, 1 H), 3.76 (d, J=17.5 Hz, 1 H), 5.33 (s, 2 H), 6.92 (d, J=8.5 Hz, 1 H), 6.94 (s, 1 H), 6.96 (s, 1 H), 6.99 (d, J=9.2 Hz, 1 H), 7.93 (s, 1 H), 8.54 (s, 1 H), 10.77 (s, 1 H).

Step 1: 1-(4-Bromo-2-ethyl-benzyl)-1*H*-[1,2,4]triazole



Triazole (275 mg, 3.99 mmol) dissolved in anhydrous DMF (15 mL) was treated with NaH (60%, 153 mg). After 5 min, 4-bromo-1-bromomethyl-2-ethyl-benzene was added. The reaction mixture was heated to 75 °C for 5 hours before it was cooled to room temperature. The mixture was diluted with Et_2O and washed with H_2O, brine, dried over $MgSO_4$. The solvent was removed in vacuo to afford the desired product (580 mg, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (t, J=7.5 Hz, 3 H), 2.66-2.73 (m, 2 H), 5.46 (s, 2 H), 7.01-7.04 (m, 1 H), 7.39-7.46 (m, 2 H), 7.97-8.01 (m, 2 H).

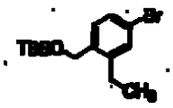
Example A(111): 6-Cyclopentyl-3-[(3,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-methyl]-6-[2-(3-ethyl-4-methylphenyl)-ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



To a solution of 6-[2-cyclopentyl-4-(3-ethyl-4-methyl-phenyl)-2-hydroxy-butyl]-2,2-dimethyl-[1,3]dioxin-4-one (1.0 g, 1.94 mmol) K_2CO_3 (1.07 g, 7.75 mmol) was added. The mixture was heated to 45 °C for 45 min before it was cooled down to room temperature. The reaction was diluted with H_2O and washed with isopropyl ether. The aqueous was acidified to pH 1 with 1.0 N HCl and extracted with EtOAc. The organic layer was washed with H_2O, brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford the desired product. (0.63 g, 71% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98(t, J=7.5 Hz, 3 H), 1.32-1.84 (m, 8 H), 2.04 (m, 2 H), 2.12 (s, 3 H), 2.33-2.61 (m, 12 H), 2.71 (d, J=17.5 Hz, 1 H), 3.64 (d, J=16.0 Hz, 1 H), 3.74 (d, J=16.2 Hz, 1 H), 6.83 (d, J=7.7 Hz, 1 H), 6.84 (s, 1 H), 6.92 (d, J=7.3 Hz, 1 H), 6.96 (s, 1 H), 10.75 (s, 1 H).

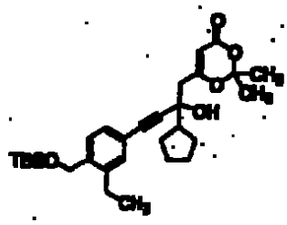
Step 1: (4-Bromo-2-ethyl-benzyloxy)-tert-butyl-dimethyl-silane

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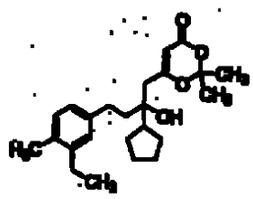
To a solution of (4-bromo-2-ethyl-phenyl)-methanol in anhydrous DMF was added TBSCl (1.5 eq.) and Imidazole (1.5 eq). The mixture was stirred at that temperature for 12 hours before it was diluted with water. The mixture was extracted with Et_2O and the combined organic layers were washed with H_2O, brine, dried over $MgSO_4$. The solvent was removed in *vacuo* to give the desired product. (93% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 0.09 (s, 6 H), 0.92 (s, 9 H), 1.20 (t, *J*=7.5 Hz, 3 H), 2.57 (q, *J*=7.5 Hz, 2 H), 4.57 (s, 2 H), 7.29 (s, 3 H).

Step 2: 6-[4-[4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-ethyl-phenyl]-2-cyclopentyl-2-hydroxy-but-3-ynyl]-2,2-dimethyl-[1,3]dioxin-4-one



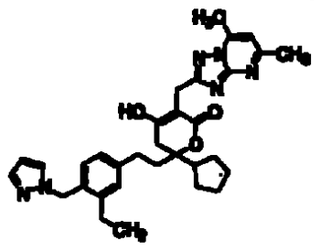
To a solution of (4-bromo-2-ethyl-benzyloxy)-*tert*-butyl-dimethyl-silane (1.0 g, 3.05 mmol) and 6-(2-cyclopentyl-2-hydroxybut-3-ynyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (871 mg, 2.84 mmol) diisopropylamine (7 mL) and DMF (7 mL) was added $PdCl_2(PPh_3)_2$ (71 mg, 4 mol%) and CuI (14 mg, 3 mol%). The mixture was purged with Ar and heated to 90 °C for 30 min before it was cooled down to room temperature. The reaction was diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with H_2O, brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column flash chromatography (SiO_2, 5-30% EtOAc in hexanes) to afford the desired product (1.0g, 60% yield). ^1H NMR (300 MHz, $CDCl_3$): δ -0.10 (s, 3H), 0.00 (s, 3 H), 0.83 (s, 9 H), 1.11 (t, J= 7.5 Hz, 3 H), 1.49-1.74 (m, 8 H), 1.82 (s, 3 H), 1.84 (s, 3 H), 2.11-2.18 (m, 1 H), 2.44-2.62 (m, 4 H), 4.63 (s, 2 H), 5.37 (s, 1 H), 7.09-7.13 (m, 2 H), 7.28-7.31 (m, 1 H).

Step 3: 6-[2-Cyclopentyl-4-(3-ethyl-4-methyl-phenyl)-2-hydroxy-butyl]-2,2-dimethyl-[1,3]dioxin-4-one



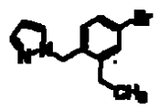
To a solution of 6-[4-[4-(tert-butyl-dimethyl-silanyloxymethyl)-3-ethyl-phenyl]-2-cyclopentyl-2-hydroxy-but-3-ynyl]-2,2-dimethyl-[1,3]dioxin-4-one (1.0 g) in EtOH (50 mL) was added $Pd(OH)_2$ (20 wt %, 100 mg). The reaction was stirred under H2 atmosphere for 15 hours. The reaction was filtered through a pad of celite and the solvent was removed under reduced pressure to afford the desired product. ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, J = 7.5 Hz, 3 H), 1.43-1.69 (m, 8 H), 1.71 (s, 6 H), 1.79-1.85 (m, 2 H), 2.05-2.16 (m, 1 H), 2.27 (s, 3 H), 2.44-2.86 (m, 6 H), 5.37 (s, 1 H), 6.89-6.95 (m, 2 H), 7.04-7.08 (m, 1 H).

Example A(112): 8-Cyclopentyl-3-[[5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]methyl]-6-[3-ethyl-4-(1H-pyrazol-1-ylmethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



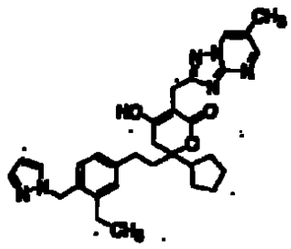
The title compound was prepared analogously to example A(1), where 1-(4-bromo-2-ethyl-benzyl)-1*H*-pyrazole from step 1 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^1H NMR (400 MHz, DMSO-d_6): δ 1.11 (t, J=7.3 Hz, 3 H), 1.48-1.80 (m, 8 H), 2.16 (m, 2 H), 2.48 (s, 3 H), 2.51-2.74 (m, 9 H), 2.89 (d, J=17.4 Hz, 1 H), 3.81 (d, J=15.9 Hz, 1 H), 3.92 (d, J=16.1 Hz, 1 H), 5.41 (s, 2 H), 6.36 (t, J=2.0 Hz, 1 H), 6.98 (d, J=8.3 Hz, 1 H), 7.11 (m, 3 H), 7.56 (s, 1 H), 7.79 (d, J=2.1 Hz, 1 H), 10.95 (s, 1 H).

Step 1: 1-(4-Bromo-2-ethyl-benzyl)-1*H*-pyrazole



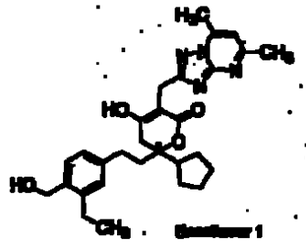
A solution of pyrazole (616 mg, 9.1 mmol) in anhydrous DMF (30 mL) was treated with naH (60%, 362 mg). 4-Bromo-1-bromomethyl-2-ethyl-benzene (2.5 g, 9.1 mmol) was added and the resulting solution was stirred at 80 °C for 13 hours before it was cooled down to room temperature. The mixture was diluted with H_2O, extracted with Et_2O. The combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the desired product (1.92 g, 80% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 1.15 (t, J=7.5 Hz, 3 H), 2.59-2.68 (m, 2 H), 5.30 (s, 2 H), 6.26-6.28 (m, 1 H), 6.86-6.88 (m, 1 H), 7.29-7.32 (m, 2 H), 7.37-7.38 (m, 1 H), 7.54-7.55 (m, 1 H).

Example A(113): 6-Cyclopentyl-6-[2-[3-ethyl-4-(1H-pyrazol-1-ylmethyl)phenyl]ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(112) where 8-methyl[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde was substituted in place of 5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde. ^{1}H NMR (400MHz, DMSO-d_6): δ 0.89 (t, J=7.6 Hz, 3 H), 1.41-1.54 (m, 6 H), 1.89 (m, 2 H), 2.21 (s, 3 H), 2.27-2.52 (m, 6 H), 2.84 (d, J=17.7 Hz, 1 H), 3.59 (d, J=15.9 Hz, 1 H), 3.67 (d, J=15.6 Hz, 1 H), 5.17 (s, 2 H), 6.12 (t, J=15.9 Hz, 1 H), 6.74 (d, J=7.6 Hz, 1 H), 6.87 (d, J=7.8 Hz, 1 H), 6.90 (d, 1 H), 7.31 (s, 1 H), 7.54 (d, J=2.2 Hz, 1 H), 8.59 (d, J=2.2 Hz, 1 H), 8.80 (s, 1 H), 10.72 (s, 1 H).

Example A(114): Enantiomer 1 of 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(hydroxymethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (

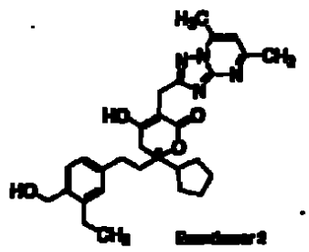


Enantiomer 1

The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(hydroxymethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (Example B(33)) (by chiral HPLC (ChiralPac OJ-H, 100 bar, 30% MeOH) ; r.t.= 2.7 min; 100% ee.

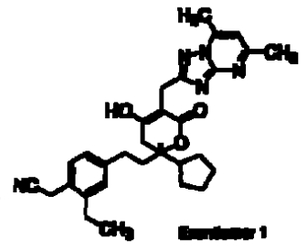
Example A(115): Enantiomer 2 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(hydroxymethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one

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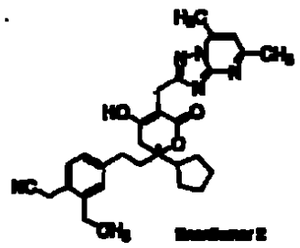
The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(hydroxymethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (Example B(33)) by chiral HPLC (ChiralPac OJ-H, 100 bar, 30% MeOH) . r.t.= 3.9 min, 100% ee.

Example A(116): Enantiomer 1 of [4-(2-[2-Cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenyl]acetonitrile



The title compound was separated from racemic [4-(2-[2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenyl]acetonitrile (Example A(101)) by chiral HPLC (ChiralPac AD-H, 140 bar, 50% MeOH) . r.t.= 3.4 min, 100% ee.

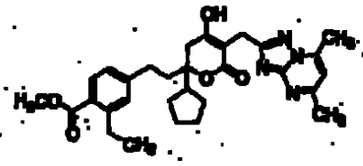
Example A(117): Enantiomer 2 of [4-(2-[2-Cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylphenyl]acetonitrile (



The title compound was separated from racemic [4-(2-[2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-

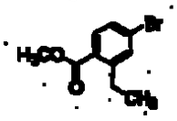
yl)ethyl)-2-ethylphenyl]acetonitrile (Example A(101)) by chiral HPLC (ChiralPac AD-H, 140 bar, 50% MeOH) . r.t.= 4.7 min, 100% ee.

Example A(118): Methyl 4-(2-[2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5-oxo-5,6-dihydro-2H-pyran-3-yl]ethyl)-3-ethylbenzoate



The title compound was prepared analogously to example A(1) where 4-bromo-2-ethyl-benzoic acid methyl ester from step 1 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (t, J=7.5 Hz, 3 H), 1.38 (s, 1 H), 1.69 (m, 10 H), 2.00 (m, 2 H), 2.57 (m, 1 H), 2.68 (s, 3 H), 2.72 (m, 2 H), 2.76 (s, 3 H), 2.92 (q, J=7.4 Hz, 2 H), 3.85 (s, 3 H), 4.08 (d, J=2.8 Hz, 2 H), 6.85 (s, 1 H), 7.00 (m, 2 H), 7.75 (d, J=7.7 Hz, 1 H). HRMS calcd for $C_{32}H_{39}N_3O_5$ $(M+H)^+$: 538.2769, found 538.2774.

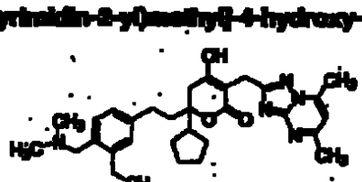
Step 1: 4-Bromo-2-ethyl-benzoic acid methyl ester



To a solution of 4-bromo-2-ethyl-benzoic acid (1.35g, 5.89 mmol) in MeOH (40 mL) was added H_2SO_4 (1 drop). The mixture was stirred at 80 °C for 48 hours, at which time the volatiles were removed *in vacuo*. The residue was dissolved in Et_2O, washed with sat'd $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to a clear oil (1.01g, 70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J=7.5 Hz, 3 H), 2.95 (q, J=7.5 Hz, 2 H), 3.87 (s, 3 H), 7.36 (dd, J=8.3, 2.1 Hz, 1 H), 7.42 (d, J=2.1 Hz, 1 H), 7.72 (d, J=8.3 Hz, 1 H).

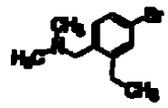
Example A(119): 6-Cyclopentyl-6-(2-{4-[(dimethylamino)methyl]-3-ethylphenyl}ethyl)-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1) where (4-bromo-2-ethyl-benzyl)-dimethyl-amine from step 1 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (t, J=7.5 Hz, 3 H), 1.38 (s, 1 H), 1.55 (s, 5 H), 1.69 (s, 2 H), 2.10 (s, 2 H), 2.49 (m, 7 H), 2.54 (s, 3 H), 2.65 (dd,

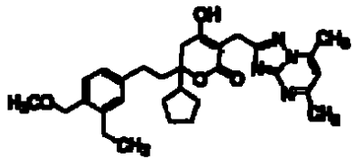
J=15.7, 8.2 Hz, 4 H), 2.74 (s, 3 H), 2.76 (s, 3 H), 3.74 (q, J= 14.8 Hz, 2 H), 4.27 (d, J=5.5 Hz, 2 H), 7.04 (s, 1 H), 7.19 (m, 2 H), 7.35 (d, J=7.7 Hz, 1 H). Anal. Calcd. For $C_{21}H_{21}N_5O_3$•2.7 TFA: C, 52.07; H, 5.25; N, 5.34. Found: C, 51.73; H, 5.56; N, 5.20.

Step 1: (4-Bromo-2-ethyl-benzyl)-dimethyl-amine



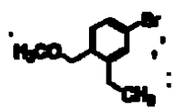
To a solution of 4-bromo-1-bromomethyl-2-ethyl-benzene (1.12g, 4.03 mmol) in MeOH (20 mL) was added dimethylamine (2.5 mL, 40% solution in water). The mixture was stirred for 1 hour, at which time the volatiles were removed *in vacuo*. The residue was dissolved in EtOAc, washed with H_2O, dried over $MgSO_4$, and concentrated to a clear oil (0.910g, 93%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, J=7.5 Hz, 3 H), 2.21 (s, 6 H), 2.69 (q, J=7.5 Hz, 2 H), 3.32 (s, 2 H), 7.14 (m, 1 H), 7.28 (m, 2 H).

Example A(120): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5-(2-[3-ethyl-4-(methoxymethyl)phenyl]ethyl)-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1) where 4-bromo-2-ethyl-1-methoxymethyl-benzene from step 1 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^1H NMR (300 MHz, DMSO): δ 1.15 (t, J=7.5 Hz, 3 H), 1.45 (s, 1 H), 1.53 (s, 5 H), 1.78 (s, 2 H), 2.05 (s, 6 H), 2.60 (m, 10 H), 3.35 (s, 3 H), 3.56 (q, J=16.2 Hz, 2 H), 4.44 (s, 2 H), 5.52 (s, 1 H), 7.09 (d, J=8.1 Hz, 2 H), 7.24 (d, J=7.7 Hz, 1 H). Anal. Calcd. For $C_{29}H_{39}N_5O_4$•0.2 TFA: C, 67.43; H, 7.11; N, 10.35. Found: C, 67.73; H, 7.16; N, 10.46.

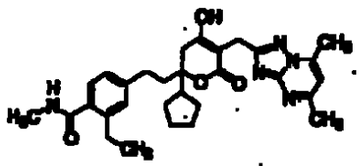
Step 1: 4-Bromo-2-ethyl-1-methoxymethyl-benzene



To a solution of (4-bromo-2-ethyl-phenyl)-methanol (0.700g, 3.25 mmol) in DMF (30 mL) was added NaH (0.156g, 60% dispersion in mineral oil, 3.90 mmol) followed by MeI (0.22 mL, 3.58 mmol). The mixture was stirred for 16 hours and then partitioned between H_2O and EtOAc. The aqueous layer was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated to a yellow oil. Purification by flash column chromatography

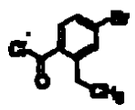
(0% to 4% EtOAc in hexanes) gave the product as a clear oil (0.51g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (t, J=7.6 Hz, 3 H), 2.58 (q, J=7.5 Hz, 2 H), 3.32 (s, 3 H), 4.35 (s, 2 H), 7.12 (m, 1 H), 7.24 (m, 1 H), 7.27 (d, J=2.1 Hz, 1 H).

Example A(121): 4-(2-[8-cyclopentyl-5-(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-ethyl-N-methylbenzamide



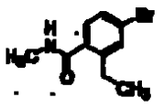
The title compound was prepared analogously to example A(1) , where 4-bromo-2-ethyl-N-methyl-benzamide from step 2 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example.^{1}H NMR (300 MHz, DMSO): δ 1.09 (t, J=7.4 Hz, 3 H), 1.41 (s, 1 H), 1.56 (s, 6 H), 1.72 (s, 2 H), 2.12 (d, J=7.0 Hz, 2 H), 2.48 (m, 2H), 2.55 (s, 3 H), 2.65 (m, 5 H), 2.75 (d, J=4.3 Hz, 3 H), 2.82 (m, 1 H), 3.18 (s, 2 H), 3.80 (q, J=17.3 Hz, 2 H), 7.05 (s, 1 H), 7.11 (m, 2 H), 7.21 (m, 1 H), 8.10 (d, J=4.5 Hz, 1 H). Anal. Calcd. For $C_{32}H_{38}N_4O_4$•1.5 TFA: C, 58.40; H, 5.52; N, 9.97. Found: C, 58.66; H, 5.57; N, 9.97.

Step 1: 4-Bromo-2-ethyl-benzoyl chloride



A solution of 4-bromo-2-ethyl-benzoic acid (1.72g, 7.51 mmol) in $SOCl_2$ (50 mL) was heated to 90 °C and stirred for 2 hours. The volatiles were removed *in vacuo* to yield a brown solid (1.80g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J=7.4 Hz, 3 H), 2.89 (q, J=7.5 Hz, 2 H), 7.49 (m, 2 H), 8.03 (d, J=9.0 Hz, 1 H).

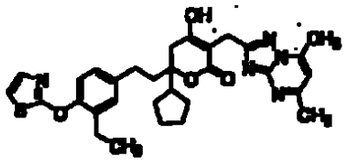
Step 2: 4-Bromo-2-ethyl-N-methyl-benzamide



To a solution of 4-bromo-2-ethyl-benzoyl chloride (1.00g, 4.04 mmol) in CH_2Cl_2 (20 mL) was added methylamine (0.70 mL, 40% solution in water, 8.08 mmol). The mixture was stirred for 3 hours, at which time the volatiles were removed *in vacuo*. The residue was dissolved in EtOAc, washed with H_2O, dried over $MgSO_4$, and concentrated to a brown oil (0.857g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, J=7.4 Hz, 3 H), 2.75 (q, J=7.5 Hz, 2 H), 2.97 (d, J=4.9 Hz, 3 H), 5.74 (s, 1 H), 7.17 (d, J=8.1 Hz, 1 H), 7.32 (d, J=8.1 Hz, 1 H), 7.39 (s, 1 H).

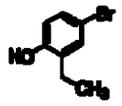
210
211

Example A(122): 6-Cyclopentyl-3-[[5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]methyl]-8-[2-[3-ethyl-4-(1,3-thiazol-2-yloxy)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



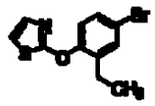
The title compound was prepared analogously to example A(1) , where 2-(4-bromo-2-ethyl-phenoxy)-thiazole from step 2 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (300 MHz, DMSO): δ 1.06 (t, J=7.4 Hz, 3 H), 1.38 (s, 1 H), 1.56 (m, J=8.4 Hz, 5 H), 1.70 (s, 2 H), 2.15 (dd, J=11.2, 5.0 Hz, 2 H), 2.80 (m, 10 H), 2.84 (m, 3 H), 2.81 (m, 1 H); 3.79 (q, J=7.4, 2 H), 7.04 (s, 1 H), 7.19 (m, 5 H). Anal. Calcd. For $C_{31}H_{39}N_4O_4S$•1.4 TFA : C, 55.39; H, 5.00; N, 9.55. Found: C, 55.12; H, 5.11; N, 9.39.

Step 1: 4-Bromo-2-ethyl-phenol



To a solution of 2-ethylphenol (2.00 g, 16.4 mmol) in $CHCl_3$ (50 mL) was added $TBABr_3$ (7.91 g, 16.4 mmol). The mixture was stirred for 20 min, at which time satd $NaHCO_3$ and satd $Na_2O_2S_2$ were added. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Filtration through SiO_2 plug (100% CH_2Cl_2) gave the product as a clear oil (2.3 g, 72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J=7.5 Hz, 3 H), 2.60 (q, J=7.5 Hz, 2 H), 4.71 (s, 1 H), 6.64 (d, J=8.5 Hz, 1 H), 7.17 (dd, J=8.5, 2.4 Hz, 1 H), 7.25 (m, 1 H).

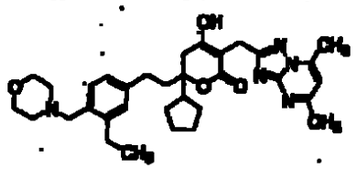
Step 2: 2-(4-Bromo-2-ethyl-phenoxy)-thiazole



To a solution of 4-bromo-2-ethyl-phenol (1.00 g, 4.97 mmol) in DMF (40 mL) was added 2-bromothiazole (0.341 mL, 3.82 mmol) and finely crushed K_2CO_3 (3.17g, 22.9 mmol). The mixture was stirred at 150 °C for 15 hours, at which time the hot solution was filtered through filter paper. The filtrate was diluted with CH_2Cl_2 and H_2O and then brought to pH 6.0 with 6.0N HCl. The aqueous layer was extracted with CH_2Cl_2 and the organic layer was washed with H_2O and brine. The organic layer was dried over Na_2SO_4 and concentrated to yield a yellow oil (1.0 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, J=7.6 Hz, 3 H), 2.62 (q, J=7.5 Hz, 2 H), 6.79 (d,

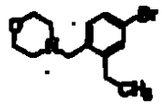
J=3.8 Hz, 1 H), 7.10 (d, J=8.5 Hz, 1 H), 7.19 (d, J=3.8 Hz, 1 H), 7.35 (dd, J=8.7, 2.4 Hz, 1 H), 7.43 (d, J=2.4 Hz, 1 H).

Example A(123): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[3-ethyl-4-(morpholin-4-ylmethyl)phenyl]ethyl}-4-hydroxy-5,6-dihydro-2H-pyran-2-one



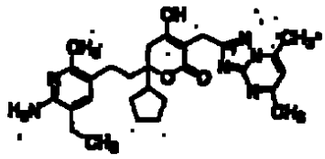
The title compound was prepared analogously to example A(1) , where 4-(4-bromo-2-ethyl-benzyl)-morpholine from step 1 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-6-propoxy-benzene in step 4 of that example. ^{1}H NMR (300 MHz, DMSO): δ 1.09 (t, J=7.4 Hz, 3 H), 1.39 (s, 1 H), 1.55 (s, 5 H), 1.89 (s, 2 H), 2.10 (m, 2 H), 2.49 (s, 7 H), 2.54 (s, 3 H), 2.83 (s, 2 H), 2.75 (m, 3 H), 3.25 (s, 4 H), 3.65 (s, 1 H), 3.74 (m, 2 H), 3.94 (d, J=10.9 Hz, 2 H), 4.33 (s, 2 H), 7.04 (s, 1 H), 7.19 (m, 2 H), 7.39 (d, J=7.7 Hz, 1 H). Anal. Calcd. For $C_{39}H_{49}N_5O_4$•2.2 TFA: C, 54.47; H, 5.53; N, 8.48. Found: C, 54.46; H, 5.57; N, 8.46.

Step 1: 4-(4-Bromo-2-ethyl-benzyl)-morpholine



To a solution of 4-bromo-1-bromomethyl-2-ethyl-benzene (3.67g, 13.2 mmol) in CH_3CN (66 mL) was added triethylamine (2.76 mL, 19.8 mmol) and morpholine (1.38 mL, 15.8 mmol). The mixture was stirred for 1.5 hours, at which time the volatiles were removed *in vacuo* to yield a pale yellow solid (3.7g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, J=7.5 Hz, 3 H), 2.40 (m, 4 H), 2.66 (q, J=7.7 Hz, 2 H), 3.40 (s, 2 H), 3.65 (m, 4 H), 7.13 (m, 1 H), 7.22 (d, J=2.1 Hz, 1 H), 7.30 (d, J=2.1 Hz, 1 H).

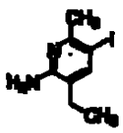
Example A(124): 6-[2-(6-Amino-5-ethyl-2-methylpyridin-3-yl)ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1) , where 3-ethyl-5-iodo-6-methyl-pyridin-2-ylamine from step 1 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-6-propoxy-benzene in step 4 of that example. ^{1}H NMR (300 MHz, DMSO): δ 1.06 (t, J=7.3 Hz, 3 H), 1.36 (s, 1 H), 1.56 (s, 5 H), 1.72 (s, 2 H), 2.03 (m, 2 H), 2.27 (s, 3 H), 2.49 (m, 8

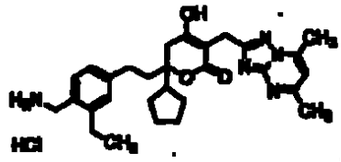
H), 2.52 (d, J=1.5 Hz, 6 H), 3.73 (q, J=16.2, 2 H), 7.04 (s, 1 H), 7.46 (s, 2 H), 7.62 (s, 1 H). HRMS calcd for $C_{28}H_{32}N_5O_3$ $(M+H)^+$: 505.2922, found 505.2936.

Step 1: 3-Ethyl-5-iodo-6-methyl-pyridin-2-ylamine



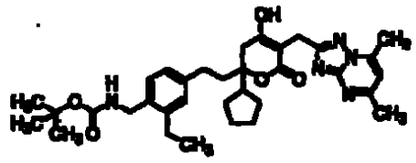
To a solution of 2-amino-3-ethyl-6-methylpyridine (3.00 g, 21.8 mmol) in DMF (100 mL) was added N-iodosuccinimide (4.86 g, 21.6 mmol). The mixture was stirred in the dark for 15 hours and then partitioned between Et_2O and H_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to yield a brown solid (4.8 g, 79%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, J=7.5 Hz, 3 H), 2.35 (q, J=7.4 Hz, 2 H), 2.49 (s, 3 H), 4.44 (s, 2 H), 7.52 (s, 1 H).

Example A(125): 6-[2-[4-(Aminomethyl)-3-ethylphenyl]ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one hydrochloride



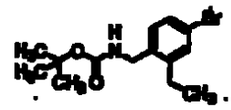
tert-Butyl 4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylbenzylcarbamate (35 mg, 0.06 mmol, example A(126)) was dissolved in dichloromethane (1 mL) and 4N HCl in dioxane (0.5 mL) and stirred at room temperature 2 h. The solution was concentrated to give an off-white solid (30 mg, 95%). ^1H NMR (300 MHz, $CDCl_3$): δ ppm 1.14 (t, J=7.54 Hz, 3 H) 1.37 - 1.49 (m, 1 H) 1.52 - 1.66 (m, 6 H) 1.67 - 1.77 (m, 2 H) 2.05 - 2.16 (m, 2 H) 2.56 (s, 4 H) 2.60 - 2.70 (m, 6 H) 2.74 - 2.80 (m, 1 H) 3.80 (d, J=14.51 Hz, 2 H) 4.02 (q, J=5.76 Hz, 2 H) 7.07 (s, 1 H) 7.13 (s, 1 H) 7.16 - 7.21 (m, 1 H) 7.32 (d, J=7.72 Hz, 1 H) 8.15 (s, 3 H) . MS (ESI): 504 $(M+H)^+$.

Example A(126): *tert*-Butyl 4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-6-ethylbenzylcarbamate



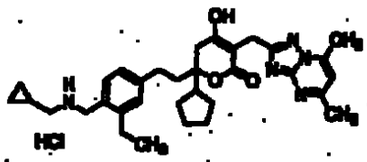
The title compound was prepared analogously to example A(1) where (4-bromo-2-ethyl-benzyl)-carbamic acid tert-butyl ester from step 1 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in that example except during workup where HCl(aq) treatments were dilute (0.1N). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.20 (t, 3 H) 1.40 (d, J=6.78 Hz, 2 H) 1.45 (s, 9 H) 1.59 (d, J=3.20 Hz, 2 H) 1.60 - 1.71 (m, 10 H) 1.88 - 1.99 (m, 2 H) 2.27 (d, J=3.20 Hz, 2 H) 2.57 - 2.69 (m, 4 H) 2.72 - 2.80 (m, 2 H) 3.39 - 3.50 (m, 2 H) 4.30 (d, J=4.52 Hz, 2 H) 4.59 - 4.73 (m, 1 H) 6.88 - 7.01 (m, 3 H) 7.16 (d, J=5.84 Hz, 1 H). MS (ESI): 532 $(M+H)^+$.

Step 1: (4-Bromo-2-ethyl-benzyl)-carbamic acid tert-butyl ester



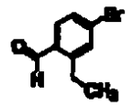
To a solution of 4-bromo-2-ethyl-benzylamine (630mg, 3.9 mmol, from step 2 of example A(131)) and triethylamine (815 µL, 5.8 mmol) in THF (5 mL) at room temperature was added di-tert-butyl dicarbonate (1.26 g, 5.8 mmol). The solution was stirred 3 h, diluted in water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, then saturated sodium chloride, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to crude off-white solid (1.4g). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.22 (t, J=7.63 Hz, 3 H) 1.45 (s, 9 H) 2.64 (q, J=7.54 Hz, 2 H) 4.29 (d, J=5.65 Hz, 2 H) 4.67 (s, 1 H) 7.12 (d, J=8.10 Hz, 1 H) 7.28 - 7.32 (m, 1 H) 7.33 (d, J=1.88 Hz, 1 H).

Example A(127): 6-Cyclopentyl-6-[2-(4-{[(cyclopropylmethyl)amino]methyl}-3-ethylphenyl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



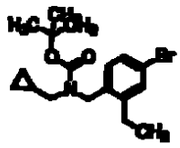
The title compound was prepared analogously to example A(1) where crude (4-bromo-2-ethyl-benzyl)-cyclopropylmethyl-carbamic acid tert-butyl ester from step 2 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in that example. ^{1}H NMR (300 MHz, MeOH): δ ppm 0.40 - 0.48 (m, 2 H) 0.70 - 0.78 (m, 2 H) 1.22 (t, J=7.54 Hz, 3 H) 1.45 - 1.57 (m, J=7.35 Hz, 1 H) 1.58 - 1.70 (m, 5 H) 1.73 - 1.80 (m, J=12.06, 4.14 Hz, 2 H) 2.08 - 2.18 (m, 2 H) 2.50 (s, 1 H) 2.69 - 2.78 (m, 12 H) 3.00 (d, J=7.54 Hz, 2 H) 3.61 - 3.68 (m, 1 H) 4.02 (d, J=3.20 Hz, 2 H) 4.24 (s, 2 H) 7.13 - 7.20 (m, 2 H) 7.56 (d, J=7.91 Hz, 1 H) 7.42 (s, 1 H). MS (ESI): 558 $(M+H)^+$.

Step 1: 4-Bromo-2-ethyl-benzaldehyde



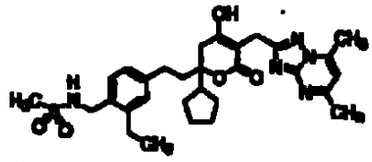
Morpholine-*N*-oxide (5.0 g, 43 mmol) was stirred in dichloromethane (30 mL) over 3A sieves 30 min under N_2 atmosphere. (4-Bromo-2-ethyl-phenyl)-methanol (3.1g, 14.4 mmol), then tetrapropylammonium perruthenate (250 mg, 0.72 mmol) was added. The solution was stirred 2h then filtered through a plug of silica. The silica was washed with 30% ethyl acetate in hexanes, and the organics were pooled. The solution was concentrated *in vacuo* to give a light yellow oil (3.4 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.28 (t, *J*=7.54 Hz, 3 H) 3.04 (q, *J*=7.54 Hz, 2 H) 7.47 (d, *J*=1.70 Hz, 1 H) 7.49 - 7.58 (m, 1 H) 7.69 (d, *J*=8.29 Hz, 1 H) 10.23 (s, 1 H).

Step 2: ((4-Bromo-2-ethyl-benzyl)-cyclopropylmethyl-carbamic acid tert-butyl ester



To 4-bromo-2-ethyl-benzaldehyde (3.0 g, 13.4 mmol) and cyclopropyl methylamine (1.0 g, 14.1 mmol) in dichloromethane (150 mL) was added magnesium sulfate (anhydrous, 200 mg) then sodium cyanoborohydride (2.2g, 35 mmol). The mixture was stirred at room temperature 16 h. The mixture was diluted in water and partitioned. The organic layer was washed with saturated sodium chloride, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a crude colorless oil (3.44g). The residue was redissolved in dichloromethane (100 mL) and triethylamine (3.6 mL, 26 mmol) then di-tert-butyl dicarbonate (3.5 g, 16.25 mmol) was added. The solution was stirred at room temperature for 2 h, then was diluted in water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, then saturated sodium chloride, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give (4-bromo-2-ethyl-benzyl)-cyclopropylmethyl-carbamic acid tert-butyl ester (3.6g) as a crude oil.

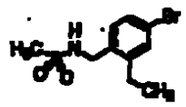
Example A(128): N-[4-(2-{2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-ethylbenzyl]methanesulfonamide



The title compound was prepared analogously to example A(1) where *N*-(4-bromo-2-ethyl-benzyl)-methanesulfonamide from step 1 below was substituted in place of 1-benzyloxy-2-

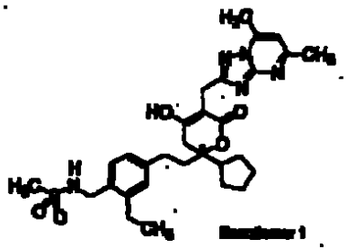
ethyl-4-iodo-5-propoxy-benzene in that example. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.21 (t, J=7.54 Hz, 3 H) 1.36 - 1.46 (m, 1 H) 1.52 - 1.67 (m, 7 H) 1.96 - 2.09 (m, 2 H) 2.36 (s, 1 H) 2.49 - 2.57 (m, 1 H) 2.62 - 2.73 (m, 6 H) 2.79 (s, 3 H) 2.89 (s, 3 H) 4.02 - 4.15 (m, 2 H) 4.27 - 4.32 (m, 2 H) 4.32 - 4.40 (m, 1 H) 5.30 (s, 1 H) 6.85 (s, 1 H) 6.98 - 7.03 (m, 2 H) 7.19 (d, J=7.72 Hz, 1 H). MS (ESI): 592 $(M+H)^+$.

Step 1: *N*-(4-Bromo-2-ethyl-benzyl)-methanesulfonamide



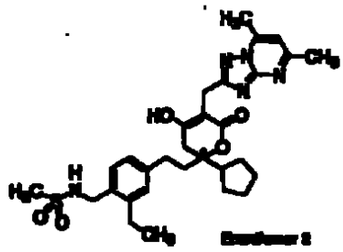
To 4-bromo-2-ethyl-benzylamine (650mg, 3 mmol) and triethylamine (500 µL, 3.6 mmol) in dichloromethane (5 mL) at room temperature was added methanesulfonyl chloride (283 µL, 3.6 mmol). The solution was stirred 1 h, diluted in water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, then saturated sodium chloride, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to an off-white solid (880 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.25 (t, J=7.54 Hz, 3 H) 2.69 (q, J=7.54 Hz, 2 H) 2.80 (s, 3 H) 4.27 - 4.31 (m, 2 H) 4.40 - 4.50 (m, 1 H) 7.21 (d, J=8.10 Hz, 1 H) 7.32 - 7.40 (m, 2 H).

Example A(129): Enantiomer 1 of N-[4-(2-[2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylbenzyl]methanesulfonamide



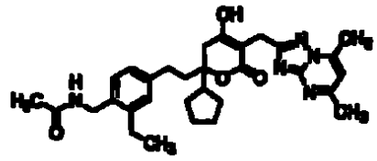
The title compound was separated from racemic N-[4-(2-[2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylbenzyl]methanesulfonamide (Example A(128)) using chiral HPLC (Chiralpak OJ-H, 120 bar, 25% MeOH). (4.819 min retention time, 100% ee)

Example A(130): Enantiomer 2 of N-[4-(2-[2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylbenzyl]methanesulfonamide



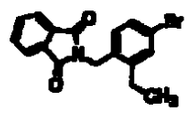
The title compound was separated from racemic N-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylbenzyl]methanesulfonamide (Example A(128)) using chiral HPLC (Chiralpak OJ-H, 120 bar, 25% MeOH). (6.413 min retention time, 100% ee)

Example A(131): N-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylbenzyl]acetamide



The title compound was prepared analogously to example A(1) where *N*-(4-bromo-2-ethyl-benzyl)-acetamide from step 3 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in that example. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.18 (t, *J*=7.54 Hz, 3 H) 1.40 (dd, *J*=8.19, 6.12 Hz, 1 H) 1.51 - 1.57 (m, 7 H) 1.97 - 2.05 (m, 6 H) 2.32 - 2.44 (m, 1 H) 2.56 (d, *J*=8.58 Hz, 1 H) 2.58 - 2.73 (m, 6 H) 2.79 (s, 3 H) 4.02 - 4.15 (m, 2 H) 4.40 (d, *J*=5.09 Hz, 2 H) 5.51 (s, 1 H) 6.85 (s, 1 H) 6.94 - 7.02 (m, 2 H) 7.12 (d, *J*=7.72 Hz, 1 H). MS (ESI): 548 $(M+H)^+$.

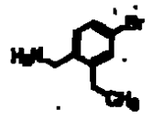
Step 1: 2-(4-Bromo-2-ethyl-benzyl)-isoindole-1,3-dione



To 4-bromo-1-bromomethyl-2-ethyl-benzene (4.0 g, 14.2 mmol) in dimethylformamide (100 mL) at room temperature was added potassium phthalimide (2.9g, 15.6 mmol), and the solution was heated at 80°C for 5 h. The solution was cooled to room temperature and poured into water. The aqueous solution was extracted with ethyl acetate. The pooled organics were washed with saturated sodium chloride, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to a yellow solid (4.0 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.27 (t, *J*=7.54 Hz, 3 H) 2.85 (q,

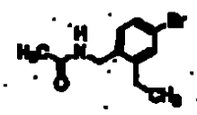
J=7.80 Hz, 2 H) 4.84 (s, 2 H) 7.14 - 7.18 (m, 1 H) 7.24 - 7.27 (m, 1 H) 7.34 (d, J=2.07 Hz, 1 H) 7.73 (dd, J=5.46, 3.01 Hz, 2 H) 7.86 (dd, J=5.56, 3.11 Hz, 2 H).

Step 2: 4-Bromo-2-ethyl-benzylamine



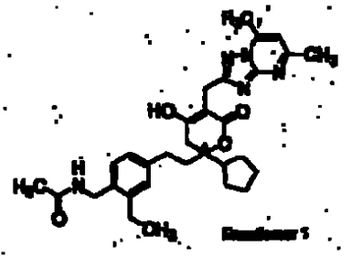
2-(4-Bromo-2-ethyl-benzyl)-isoindole-1,3-dione (4g, 11.7 mmol) and hydrazine (1.8 mL, 58.3 mmol) in chloroform:ethanol (1:1.5, 250 mL) were refluxed for 4 h. The mixture was cooled to room temperature and filtered through a pad of celite. The solution was diluted in water and partitioned. The organic layer was washed with water, saturated sodium bicarbonate, then saturated sodium chloride, dried (Na_2SO_4), filtered, and then concentrated *in vacuo* to a yellow oil (2.2 g, 88%). ^1H NMR (300 MHz, $CDCl_3$): δ ppm 1.23 (t, J=7.54 Hz, 3 H) 1.65 (s, 2 H) 2.66 (q, J=7.60 Hz, 2 H) 3.84 (s, 2 H) 7.19 - 7.23 (m, 1 H) 7.30 - 7.34 (m, 2 H).

Step 3: *N*-(4-Bromo-2-ethyl-benzyl)-acetamide



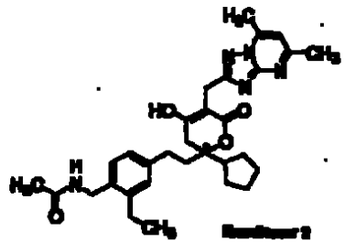
To 4-bromo-2-ethyl-benzylamine (700mg, 3.3 mmol) and triethylamine (600 µL, 4.3 mmol) in dichloromethane (5 mL) at room temperature was added acetyl chloride (310 µL, 4.5 mmol). The solution was stirred for 1 h, diluted in water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, then saturated sodium chloride, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to an off-white solid (820 mg, 97%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, J=7.54 Hz, 3 H) 2.00 (s, 3 H) 2.62 (q, J=7.54 Hz, 2 H) 4.38 (d, J=5.46 Hz, 2 H) 5.59 (s, 1 H) 7.09 (d, J=8.10 Hz, 1 H) 7.26 - 7.31 (m, 1 H) 7.34 (d, J=1.86 Hz, 1 H).

Example A(132): Enantiomer 1 of N-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl}ethyl)-2-ethylbenzyl]acetamide



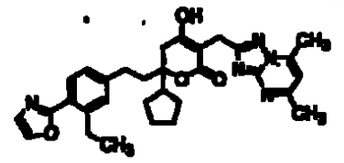
The title compound was separated from racemic N-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylbenzyl]acetamide (Example A(131)) using chiral HPLC (Chiralpak AS-H, 140 bar, 50% MeOH). (4.924 min retention time, 100% ee).

Example A(133): Enantiomer 2 of N-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylbenzyl]acetamide



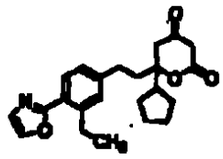
The title compound was separated from racemic N-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-ethylbenzyl]acetamide (Example A(131)) using chiral HPLC (Chiralpak AS-H, 140 bar, 50% MeOH). (6.947min retention time, 100% ee).

Example A(134): 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



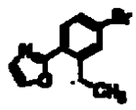
The title compound was prepared analogously to example A(1) where 6-cyclopentyl-6-[2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl]dihydro-2H-pyran-2,4(3H)-dione (Example A(135)) was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione in that example. Yield (35 mg, 6%). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.19 (t, J=7.44 Hz, 3 H) 1.50 - 1.57 (m, 3 H) 1.57 - 1.84 (m, J=8.29 Hz, 2 H) 1.85 - 1.77 (m, 3 H) 1.99 - 2.07 (m, J=17.33 Hz, 1 H) 2.33 - 2.44 (m, 1 H) 2.51 - 2.59 (m, 1 H) 2.65 (s, 3 H) 2.68 - 2.80 (m, 7 H) 3.03 (q, J=7.41 Hz, 2 H) 4.09 (s, 2 H) 6.83 (s, 1 H) 7.03 - 7.09 (m, 2 H) 7.23 (s, 1 H) 7.69 (s, 1 H) 7.80 (d, J=7.91 Hz, 1 H). MS (ESI): 542 $(M+H)^+$.

Example A(135): 6-Cyclopentyl-6-[2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl]dihydro-2H-pyran-2,4(3H)-dione



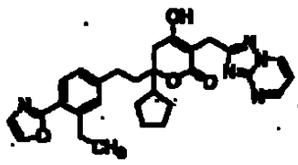
The title compound was prepared analogously to example A(2) where 2-(4-bromo-2-ethyl-phenyl)-oxazole from step 1 below was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.21 (t, *J*=7.44 Hz, 3 H) 1.42 - 1.57 (m, 2 H) 1.69 - 1.74 (m, 6 H) 1.96 - 2.04 (m, 1 H) 2.14 - 2.22 (m, 1 H) 2.24 - 2.36 (m, 1 H) 2.67 - 2.78 (m, 2 H) 2.80 (s, 2 H) 2.89 - 2.96 (m, 2 H) 3.46 (s, 2 H) 7.11 - 7.17 (m, 2 H) 7.44 - 7.53 (m, 1 H) 7.77 (d, *J*=8.29 Hz, 1 H) 7.84 (s, 1 H). MS (ESI): 392 $(M+H)^+$.

Step 1: 2-(4-Bromo-2-ethyl-phenyl)-oxazole



4-Bromo-2-ethyl-benzoic acid (6.8g, 30 mmol), diisopropylethylamine (7.8 mL, 44.7 mmol), *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HATU, 14g, 37 mmol), and aminoacetaldehyde dimethyl ether (4 mL, 37 mmol) in 2:1 dichloromethane/dimethylformamide (120 mL) 5 h at room temperature. The solution was washed with several portions of water, then 1N $HCl_{(aq)}$ and saturated sodium chloride, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to a crude light yellow oil. The residue was redissolved in Eaton's reagent (P_2O_5 in methanesulfonic acid, 100 mL), and the solution was heated at 135°C under argon for 6h. The solution was cooled to room temperature and carefully poured onto ice. The mixture was extracted with dichloromethane, and the organic layer was backwashed with saturated sodium chloride, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to a crude oil. The residue was redissolved in ethyl acetate and washed with saturated sodium bicarbonate, then saturated sodium chloride, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to pure brown liquid (3.16g, 44%) ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.24 (t, *J*=7.54 Hz, 3 H) 3.09 (q, *J*=7.54 Hz, 2 H) 7.27 (s, 1 H) 7.42 (dd, *J*=8.38, 1.98 Hz, 1 H) 7.48 (d, *J*=2.07 Hz, 1 H) 7.74 (s, 1 H) 7.81 (d, *J*=8.48 Hz, 1 H).

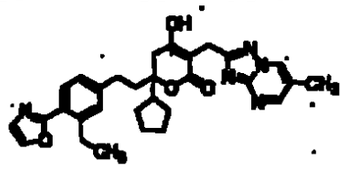
Example A(136): 6-Cyclopentyl-6-(2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl)-4-hydroxy-3-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-5,6-dihydro-2H-pyran-2-one



220
221

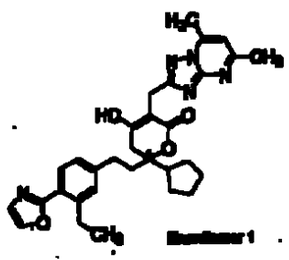
The title compound was prepared analogously to Example A(1) where 6-cyclopentyl-6-[2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl]dihydro-2H-pyran-2,4(3H)-dione (Example A(135)) was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione in that example and methoxy-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl-methanol was substituted in place of 5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde. Yield (57 mg, 11%). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.20 (t, J=7.44 Hz, 3 H) 1.53 - 1.67 (m, 6 H) 2.00 - 2.11 (m, 2 H) 2.35 - 2.47 (m, 1 H) 2.51 - 2.63 (m, 1 H) 2.65 - 2.72 (m, 2 H) 2.72 - 2.83 (m, 2 H) 3.04 (q, J=7.54 Hz, 2 H) 4.14 (d, J=3.77 Hz, 2 H) 7.04 - 7.10 (m, 2 H) 7.14 - 7.20 (m, 1 H) 7.25 (s, 1 H) 7.71 (s, 1 H) 7.82 (d, J=7.91 Hz, 1 H) 8.84 (d, J=5.46 Hz, 2 H). MS (ESI): 514 $(M+H)^+$.

Example A(137): 6-Cyclopentyl-6-[2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one



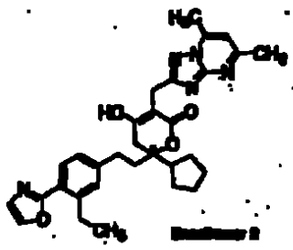
The title compound was prepared analogously to example A(1) where 6-cyclopentyl-6-[2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl]dihydro-2H-pyran-2,4(3H)-dione (Example A(135))was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione in that example and 8-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde was substituted in place of 5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde. Yield (58 mg, 11%). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.19 (t, J=7.44 Hz, 3 H) 1.40 (d, J=4.33 Hz, 1 H) 1.53 - 1.67 (m, 6 H) 2.01 - 2.10 (m, 2 H) 2.39 (s, 1 H) 2.45 - 2.49 (m, 3 H) 2.54 - 2.64 (m, 1 H) 2.71 (dd, J=11.87, 5.46 Hz, 2 H) 2.76 - 2.85 (m, 1 H) 3.01 (q, J=7.47 Hz, 2 H) 4.10 (s, 2 H) 7.05 - 7.11 (m, 2 H) 7.29 (s, 1 H) 7.73 (s, 1 H) 7.78 (d, J=7.91 Hz, 1 H) 8.61 (s, 1 H) 8.68 (d, J=2.07 Hz, 1 H). MS (ESI): 528 $(M+H)^+$.

Example A(138): Enantiomer 1 of 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



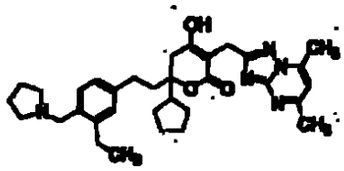
The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (Example A(134)) using chiral HPLC (Chiralpak AS-H, 140 bar, 50% MeOH). (1.968 min retention time, 100% ee).

Example A(139): Enantiomer 2 of 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



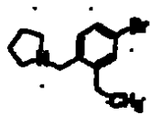
The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(1,3-oxazol-2-yl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (Example A(134)) using chiral HPLC (Chiralpak AS-H, 140 bar, 50% MeOH). (3.537 min retention time, 95% ee).

Example A(140): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(pyrrolidin-1-ylmethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1) where 1-(4-bromo-2-ethyl-benzyl)-pyrrolidine from step 1 below was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (300 MHz, DMSO): δ 1.05 (t, J=7.3 Hz, 3 H), 1.34 (s, 1 H), 1.50 (s, 5 H), 1.66 (m, 2 H), 1.81 (m, 2 H), 2.02 (m, 4 H), 2.44 (m, 7 H), 2.62 (m, 7 H), 3.07 (m, 2 H), 3.37 (m, 2 H), 3.75 (q, J=16.2 Hz, 2 H), 4.30 (d, J=5.3 Hz, 2 H), 6.99 (s, 1 H), 7.12 (m, 2 H), 7.33 (d, J=7.7 Hz, 1 H). HRMS calcd for $C_{33}H_{43}N_5O_3$ $(M+H)^+$: 558.3439, found 558.3448.

Step 1: 1-(4-Bromo-2-ethyl-benzyl)-pyrrolidine

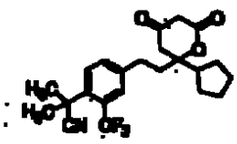


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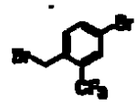
To a solution of 4-bromo-1-bromomethyl-2-ethyl-benzene (2.00g, 7.19 mmol) in CH_2Cl_2 (30 mL) was added dropwise pyrrolidine (1.19 mL, 14.4 mmol). The mixture was stirred for 15 hours, and then partitioned between Et_2O and H_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to yield a yellow oil (1.3 g, 68%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, J=7.5 Hz, 3 H), 1.76 (m, 4 H), 2.47 (m, 4 H), 2.69 (q, J=7.5 Hz, 2 H), 3.54 (s, 2 H), 7.19 (m, 1 H), 7.25 (m, 1 H), 7.29 (d, J=1.9 Hz, 1 H).

Example A(141): 2-[4-[2-(2-Cyclopentyl-4,6-dioxotetrahydro-6H-pyran-6-yl)ethyl]-2-trifluoromethyl]phenyl]-2-methylpropanenitrile



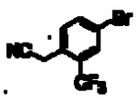
The title compound was prepared analogously to example A(2) where 2-(4-bromo-2-trifluoromethyl-phenyl)-2-methyl-propionitrile from step 3 below was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.50-1.86 (m, 14 H), 1.94-1.98 (m, 2H), 2.27-2.30 (m, 1H), 2.73-2.80 (m, 4H), 3.44 (d, J=4.3 Hz, 2 H), 7.36 (dd, J=8.2, 1.8 Hz, 1 H), 7.54 (d , J=1.8 Hz, 1 H), 7.85 (d, J=8.2 Hz, 1 H). $(M+H)^+$MS (ESI): 422 $(M+H)^+$

Step 1: 4-Bromo-1-bromomethyl-2-trifluoromethyl-benzene



A mixture of 4-methyl-3-trifluorobromobenzene (25 g, 104.59 mmol), N-bromosuccinimde (18.62 g, 104.59 mmol) and benzoyl peroxide (1.27 g, 5.23 mmol) in CCl_4 (35 mL) was heated at 90 °C for 4 hours. The reaction mixture was cooled to 0 °C and then filtered through a glass frit washing with CH_2Cl_2. The filtrate was concentrated and then purified by flash column chromatography (0% to 5% EtOAc in hexanes) to give the product as a clear oil that crystallized on standing (33.28 g, 100%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.57 (s, 2H), 7.46 (d, J=8.3 Hz, 1 H), 7.67 (d, J=8.3 Hz, 1 H), 7.78 (s, 1H).

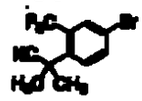
Step 2: (4-Bromo-2-trifluoromethyl-phenyl)-acetonitrile



A mixture of 4-methyl-3-trifluorobromobenzene (33.28 g, 104.261 mmol) from step 1 above , KCN (20.43 g, 313.67 mmol) and tetrabutylammonium bromide (3.37 g, 10.45 mmol) in CH_2Cl_2/H_2O 1:1 (300 mL) was stirred at room temperature for 4 hours. The layers were

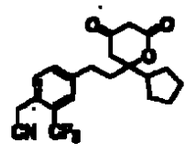
separated and the organic layer washed with H_2O (100 mL) 1N HCl (100 mL), brine, dried over Na_2SO_4 and then concentrated to a brown oil which was purified by flash column chromatography (0% to 20% EtOAc in hexanes) to give the product as a clear oil (14.9 g, 54%). ^1H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 2H), 7.57 (d, J=8.3 Hz, 1 H), 7.75 (dd, J=8.3, 2 Hz, 1 H), 7.84 (d, J=2 Hz, 1 H).

Step 3: 2-(4-Bromo-2-trifluoromethyl-phenyl)-2-methyl-propionitrile



NaH 95% (2.28 g, 94.7 mmol) was suspended in DMF (25mL) and cooled to 0 °C. (4-Bromo-2-trifluoromethyl-phenyl)-acetonitrile (5 g, 18.94 mmol) from step 2 above, was dissolved in THF (35 mL) and slowly added via cannula to the NaH suspension. The reaction mixture was stirred for 20 min. Methyl iodide (11.79 mL, 189.36 mmol) was added and the resulting mixture was stirred overnight at room temperature. Reaction was quenched with H_2O (100 mL). Solvents were removed in vacuo and residue partitioned between EtOAc and 1N HCl (100 mL). The organic phase was dried over Na_2SO_4 and evaporated. The crude organic product was purified by flash column chromatography (5% EtOAc in hexanes) to give the product (4.14 g, 75%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.8 (s, 6H), 7.46 (d, J=8.3 Hz, 1 H), 7.67 (d, J=8.3 Hz, 1 H), 7.78 (s, 1H).

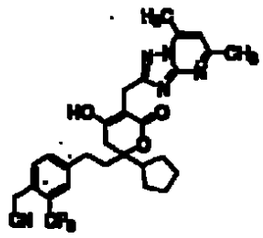
Example A(142): [4-[2-(2-Cyclopentyl-4,6-dimoxtetrahydro-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)phenyl]acetonitrile



The title compound was prepared analogously to example A(2) where 4-bromo-1-bromomethyl-2-trifluoromethyl-benzene from step 2 of example A(141) was substituted in place of 4-bromo-2-ethyl-6-methoxy-pyridine in step 6 of that example. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.46-1.62 (br m, 8 H), 1.94-1.97 (m, 2H), 2.24-2.80 (m, 1 H), 2.89-2.54 (m, 4 H), 3.44 (d, J=4.04 Hz, 2 H), 3.92 (s, 2H), 7.40 (d, J=8.08 Hz, 1 H), 7.47 (s, 1 H), 7.60-7.62 (m, 1H). MS (ESI): 394 $(M+H)^+$

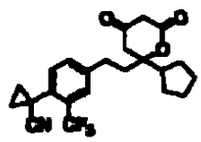
Example A(143): [4-[2-[2-Cyclopentyl-6-[(6,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-3-(fluoromethyl)phenyl]acetonitrile

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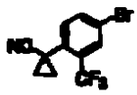
The title compound was prepared analogously to example A(1) where [4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-6H-pyran-2-yl)ethyl]-2-(trifluoromethyl)phenyl]acetonitrile (example A(142)) was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.38-1.74 (br m, 10 H), 2.13-2.23 (m, 1 H), 2.49-2.58 (m, 7 H), 2.79-2.87 (m, 3H), 3.76 (d, J=16 Hz, 1 H), 3.85 (d, J=16 Hz, 1 H), 4.16 (s, 2H), 7.06 (s, 1 H), 7.64-7.77 (m, 3H), 10.87 (s, 1 H). Anal. Calcd. For $C_{28}H_{30}F_3N_3O_3.0.5\ H_2O$: C, 61.91; H, 5.55, N, 12.45; Found: C, 62.00; H, 5.85, N, 12.66. MS (ESI): 554.1 $(M+H)^+$

Example A(144): 1-[4-[2-(2-Cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)phenyl]cyclopropanecarbonitrile



The title compound was prepared analogously to example A(2) where 1-(4-bromo-2-trifluoromethyl-phenyl)-cyclopropanecarbonitrile from step 1 below was substituted in place of 4-bromo-2-ethyl-5-methoxy-pyridine in step 6 of that example. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.41-1.43 (m, 2H), 1.53-1.77 (m, 10 H), 1.93-1.97 (m, 2H), 2.25-2.30 (m, 1 H), 2.72-2.80 (m, 4H), 3.44 (d, J=4.8 Hz, 2 H), 7.33-7.35 (m, 1 H), 7.47-7.49 (m, 2 H). MS (ESI): 420 $(M+H)^+$.

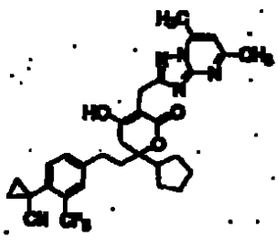
Step 1: 1-(4-Bromo-2-trifluoromethyl-phenyl)-cyclopropanecarbonitrile



To a stirred solution of (4-bromo-2-trifluoromethyl-phenyl)-acetonitrile (3.33 g, 12.61 mmol) from step 2 of example A(141), benzyltriethylammonium chloride (0.057 g, 0.25 mmol) and 1-bromo-2-chloroethane (1.57 g, 10.94 mmol), was added dropwise a solution of NaOH 40% (3 mL). The reaction mixture was stirred 6 hours at 50 °C. After this time the reaction was quenched with 1N HCl (30 mL) and extracted with EtOAC (3 x 30 mL). The organic phase was dried over Na_2SO_4 and evaporated. The crude organic product was purified by flash column chromatography (10% EtOAc in hexanes) to give the product (3.1 g, 86%) as a clear oil. ^{1}H

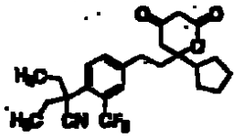
NMR (400 MHz, $CDCl_3$) δ 1.4-1.44 (m, 2H), 1.76-1.80 (m, 2H), 7.44 (d, J=8.3 Hz, 1 H), 7.69 (dd, J=8.3, 2 Hz, 1 H), 7.84 (d, J=2 Hz, 1 H).

Example A(145): 1-[4-(2-(2-Cyclopentyl-8-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-3-(trifluoromethyl)phenyl]cyclopropanecarbonitrile



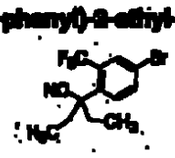
The title compound was prepared analogously to example A(1) where 1-[4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)phenyl]cyclopropanecarbonitrile (example A(144))was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.89-0.90 (m, 2H), 1.27-1.79 (m, 12 H), 2.11-2.16 (m, 1 H), 2.49-2.59 (m, 7 H), 2.76-2.80 (m, 3H), 3.75 (d, J=16 Hz, 1 H), 3.86 (d, J=16 Hz, 1 H), 7.07 (s, 1 H), 7.65-7.70 (m, 3H), 10.57 (s, 1 H). Anal. Calcd. For $C_{31}H_{34}F_3N_5O_4.1.0\ H_2O$: C, 62.30; H, 5.73, N, 11.72; Found: C, 62.40; H, 5.85, N, 11.80. MS (ESI): 590.1 $(M+H)^+$

Example A(146): 2-[4-[2-(2-Cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-3-(trifluoromethyl)phenyl]-2-ethylbutanenitrile



The title compound was prepared analogously to example A(2) where 2-(4-bromo-2-trifluoromethyl-phenyl)-2-ethyl-butyronitrile from step 1 below was substituted in place of 4-bromo-2-ethyl-6-methoxy-pyridine in step 6 of that example. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.95 (t, J=7.2 Hz, 6 H), 1.45-1.76 (m, 6 H), 1.96-2.31 (m, 7 H), 2.74-2.80 (m, 4 H), 3.44 (d, J=8.09 Hz, 2 H), 7.35 (dd, J=8.08, 1.77 Hz, 1 H), 7.56 (s, 1 H), 7.70 (d, J=8.08, Hz 1 H). MS (ESI): 450 $(M+H)^+$.

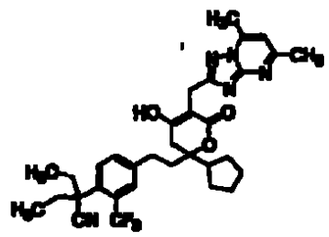
Step 1: 2-(4-Bromo-2-trifluoromethyl-phenyl)-2-ethyl-butyronitrile



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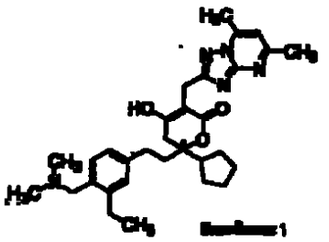
The title compound was prepared analogously to step 3 of example A(141)where iodoethane was substituted in place of methyl iodide in that example. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (t, J=7.2 Hz, 6 H), 1.3-1.4 (m, 4H), 7.46 (d, J=8.3 Hz, 1 H), 7.67 (d, J=8.3 Hz, 1 H), 7.78 (s, 1H).

Example A(147): 2-[4-[2-[2-Cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5-oxo-5,6-dihydro-2H-pyran-2-yl]ethyl]-2-(trifluoromethyl)phenyl]-2-ethylbutanenitrile



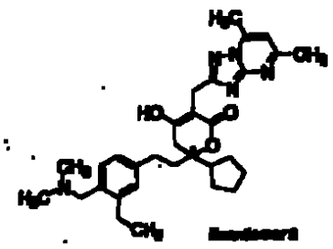
The title compound was prepared analogously to example A(1) where 2-[4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)phenyl]-2-ethylbutanenitrile (example A(146))was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.77 (t, J=7.2 Hz, 6 H), 1.29-1.62 (m, 10 H), 1.90-2.10 (m, 5 H), 2.36-2.50 (m, 7 H), 2.58-2.74 (m, 3H), 3.62 (d, J=16 Hz, 1 H), 3.74 (d, J=16 Hz, 1 H), 6.97 (s, 1 H), 7.56-7.57 (m, 3H), 10.77 (s, 1 H). MS (ESI): 610 $(M+H)^+$

Example A(148): Enantiomer 1 of 6-Cyclopentyl-6-(2-(4-[(dimethylamino)methyl]-3-ethylphenyl]ethyl)-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



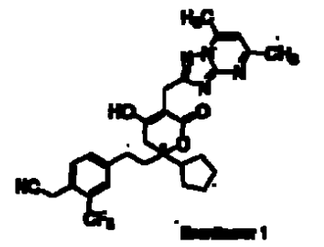
The title compound was separated from racemic 6-cyclopentyl-6-(2-(4-[(dimethylamino)methyl]-3-ethylphenyl]ethyl)-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (236 mg, Example A(119)) using chiral HPLC (Chiralpak AS-H, 140 bar, 35% MeOH w/ 0.1% triethylamine). (31.7 mg, 2.108 min retention time, 100% ee).

Example A(149): Enantiomer 2 of 6-Cyclopentyl-6-(2-[4-[(dimethylamino)methyl]-3-ethylphenyl]ethyl)-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



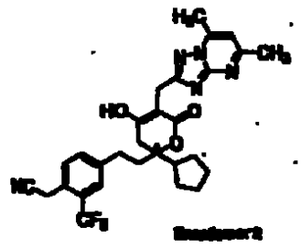
The title compound was separated from racemic 6-cyclopentyl-6-(2-[4-[(dimethylamino)methyl]-3-ethylphenyl]ethyl)-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (236 mg, Example A(119)) using chiral HPLC (Chiralpak AS-H, 140 bar, 35% MeOH w/ 0.1% triethylamine). (20.7 mg, 3.754 min retention time, 100% ee).

Example A(150): Enantiomer 1 of [4-(2-[2-Cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-(trifluoromethyl)phenyl]acetonitrile



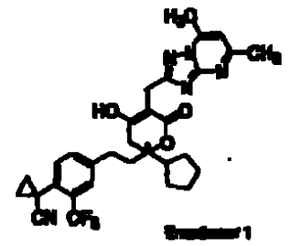
The title compound was separated from racemic [4-(2-[2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-(trifluoromethyl)phenyl]acetonitrile (490 mg, Example A(143)) using chiral HPLC (Chiralpak AS-H, 140 bar, 50% MeOH). (100 mg, 1.84 min retention time, 100% ee)

Example A(151): Enantiomer 2 of [4-(2-[2-Cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-(trifluoromethyl)phenyl]acetonitrile



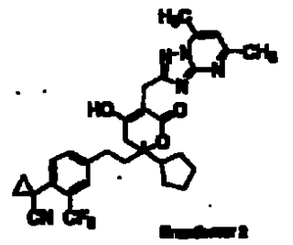
The title compound was separated from racemic [4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-(trifluoromethyl)phenyl]acetonitrile (490 mg, Example A(143)) using chiral HPLC (Chiralpak AS-H, 140 bar, 50% MeOH). (75 mg, 3.67 min retention time, 100% ee)

Example A(152): Enantiomer 1 of 1-[4-(2-[2-Cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-(trifluoromethyl)phenyl]cyclopropanecarbonitrile



The title compound was separated from racemic 1-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-(trifluoromethyl)phenyl]cyclopropanecarbonitrile (250 mg, Example A(145)) using chiral HPLC (Chiralpak AS-H, 140 bar, 50% MeOH). (95 mg, 1.66 min retention time, 100% ee)

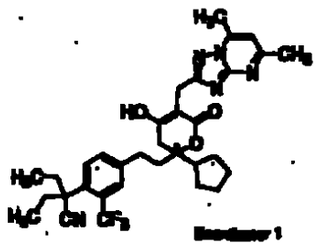
Example A(153): Enantiomer 2 of 1-[4-(2-[2-Cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-(trifluoromethyl)phenyl]cyclopropanecarbonitrile



The title compound was separated from racemic 1-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-

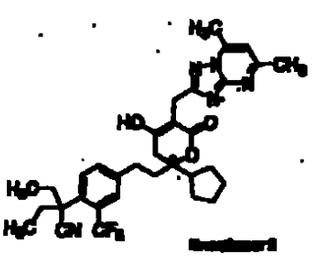
yl)ethyl)-2-(trifluoromethyl)phenyl)cyclopropanecarbonitrile (250 mg, Example A(145)) using chiral HPLC (Chiralpak AS-H, 140 bar, 50% MeOH). (87 mg, 5.35 min retention time, 100% ee)

Example A(154): Enantiomer 1 of 2-[4-(2-[2-Cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)phenyl]-2-ethylbutanenitrile



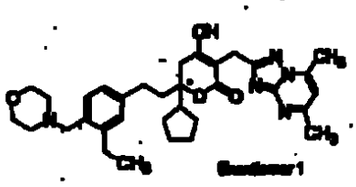
The title compound was separated from racemic 2-[4-(2-[2-Cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)phenyl]-2-ethylbutanenitrile (180 mg, Example A(147)) using chiral HPLC (Chiralpak AS-H, 140 bar, 30% MeOH). (82.27 mg, 2.47 min retention time, 100% ee)

Example A(155): Enantiomer 2 of 2-[4-(2-[2-Cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)phenyl]-2-ethylbutanenitrile



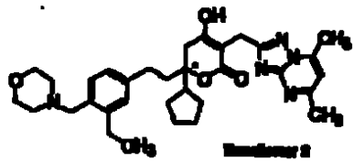
The title compound was separated from racemic 2-[4-(2-[2-Cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)phenyl]-2-ethylbutanenitrile (180 mg, Example A(147)) using chiral HPLC (Chiralpak AS-H, 140 bar, 30% MeOH). (180 mg, 7.57 min retention time, 100% ee)

Example A(156): Enantiomer 1 of 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[2-ethyl-4-(morpholin-4-ylmethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



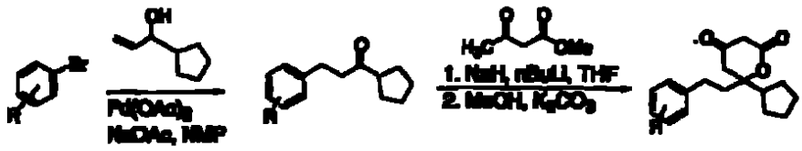
The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(morpholin-4-ylmethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (151 mg, Example A(123)) using chiral HPLC (Chiralpak AS-H, 140 bar, 40% MeOH). (32 mg, 3.302 min retention time, 100% ee)

Example A(167): Enantiomer 2 of 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(morpholin-4-ylmethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one

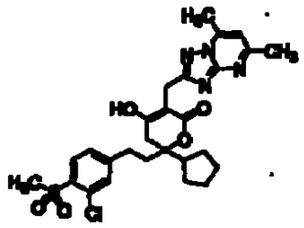


The title compound was separated from racemic 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(morpholin-4-ylmethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (151 mg, Example A(123)) using chiral HPLC (Chiralpak AS-H, 140 bar, 40% MeOH). (34 mg, 9.004 min retention time, 100% ee)

Scheme 2: Hack Route



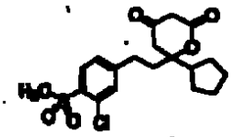
Example B(1): 6-[2-[3-Chloro-4-(methylsulfonyl)phenyl]ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1) where 6-[2-[3-chloro-4-(methylsulfonyl)phenyl]ethyl]-6-cyclopentyldihydro-2H-pyran-2,4(3H)-dione (Example B(2)) was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione in that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.45-2.22 (m, 11 H), 2.66 (s, 3 H), 2.70-2.99 (m, 7 H), 3.02 (m, 2 H), 3.26 (s, 3H), 6.99 (s, 1 H), 7.01 (s, 1 H), 7.25 (s, 1 H), 7.36 (m, 2 H). Anal. Calcd. For $C_{27}H_{31}N_4O_5S$: C, 58.01; H, 5.59; N, 10.02. Found: C, 58.05; H, 5.50; N, 9.89.

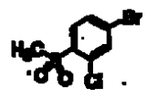
257
232

Example B(2): 6-[2-[3-Chloro-4-(methylsulfonyl)phenyl]ethyl]-6-cyclopentylidihydro-2H-pyran-2,4(3H)-dione



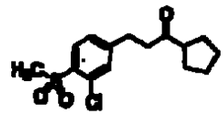
Methyl acetoacetate (1.03 mL, 9.5 mmol) was added to a cooled 0 °C suspension of NaH (0.38 g, 9.5 mmol, 60% dispersion in mineral oil) in THF (30ml). After 15 min, n-BuLi (3.8 mL, 9.5 mmol, 2.5M in hexanes) was added. The resulting dianion was stirred for an additional 30 min and then treated with a solution of 3-(3-chloro-4-methanesulfonyl-phenyl)-1-cyclopentyl-propan-1-one (1.0 g, 3.16 mmol, from step 2 below) in THF (20ml). After stirring for 30 mins at 0 °C and then at room temperature for 2 hours, the reaction mixture was quenched with 1N HCl and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to a yellow oil that was used without further purification. The oil was dissolved in methanol (100 mL), treated with potassium carbonate (1.0 g, 7.2 mmol), and refluxed under N_2 for 60 mins. The reaction mixture was partitioned between H_2O and IPE. The aqueous layer was made acidic with 1N HCl and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give the product (0.9 g, 71% yield). ^1H NMR (300MHz, $CDCl_3$): δ 1.25-2.30 (m, 11 H), 2.75-3.16 (m, 6 H), 3.26 (s, 3H), 7.21 (s, 1 H), 7.40 (m, 2 H)

Step 1: 4-Bromo-2-chloro-1-methanesulfonyl-benzene



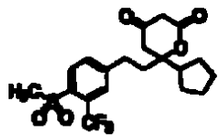
Hydrazine monohydrate (1.51mL, 48 mmol) was added to a cooled 0 °C solution of 4-bromo-2-chlorobenzenesulfonyl chloride (5g, 17.2 mmol) dissolved in THF (50 mL). The reaction was stirred at room temperature for 2 hours and then the solvent was removed in vacuo to give a white solid. The solid was dissolved in EtOH (100 mL) and treated with sodium acetate (6.56 g, 80 mmol) followed by methyl iodide (4.9 mL, 79 mmol). The reaction mixture was refluxed for 18 hours. The solvent was removed in vacuo to give a residue that was partitioned between 1 N HCl and EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The crude mixture was purified by flash column chromatography to give the product (1.5 g, 32%). ^1H NMR (300 MHz, $CDCl_3$): δ 3.28 (s, 3 H), 7.83 (dd, J=8.5, 1.9 Hz, 2 H), 7.74 (d, J=1.9 Hz, 1 H), 8.02 (d, J=8.5 Hz, 1 H).

Step 2: 3-(3-Chloro-4-methanesulfonyl-phenyl)-1-cyclopentyl-propan-1-one



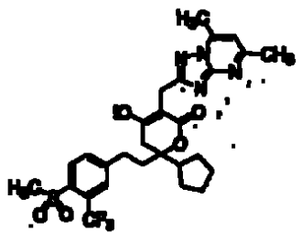
A mixture of 4-bromo-2-chloro-1-methanesulfonyl-benzene (1.5 g, 5.6 mmol), 1-cyclopentyl-2-propen-1-ol (0.88 g, 6.96 mmol) and sodium acetate (0.57 g, 6.9 mmol) in DMAC (20 mL) was purged with N_2 for 30 mins. Palladium (II) acetate (25 mg, 0.11 mmol) was added and the mixture was heated to 90 °C under N_2 for 16 hours. The reaction mixture was partitioned between 1N HCl and EtOAc. The organic layers were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated to a brown oil. Purification by flash column chromatography (0% to 20% EtOAc in hexanes) gave the desired product (1.2g, 69%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.58-1.85 (br m, 8 H), 2.83 (m, 3 H), 2.96 (t, J=7.5 Hz, 2 H), 3.25 (s, 3 H), 7.29 (dd, J=8.1, 1.5 Hz, 1 H), 7.39 (d, J=1.5 Hz, 1 H), 8.04 (d, J=8.1 Hz, 1 H).

Example B(3): 6-Cyclopentyl-6-[2-[4-(methylsulfonyl)-3-(trifluoromethyl)phenyl]ethyl]-dihydro-2H-pyran-2,4(3H)-dione



The title compound was prepared analogously to example B(2): where 4-bromo-1-methanesulfonyl-2-trifluoromethyl-benzene was substituted in place of 4-bromo-2-chlorobenzenesulfonyl chloride in step 1 of that example. ^1H NMR (300MHz, $CDCl_3$): δ 1.50-2.40 (m, 11 H), 2.80-3.46 (m, 9 H), 7.52 (d, J=1.56 Hz, 1 H), 7.78 (s, 1 H), 7.90 (d, J=1.08 Hz, 1 H).

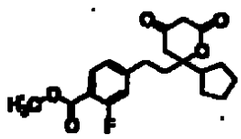
Example B(4): 6-Cyclopentyl-6-[[5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]methyl]-4-hydroxy-6-[2-[4-(methylsulfonyl)-3-(trifluoromethyl)phenyl]ethyl]-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example A(1) where 6-cyclopentyl-6-(2-[4-(methylsulfonyl)-3-(trifluoromethyl)phenyl]ethyl]dihydro-2H-pyran-2,4(3H)-dione (Example B(3): was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione in that example. ^1H NMR (400MHz, $CDCl_3$): δ 1.35-2.19 (m, 11

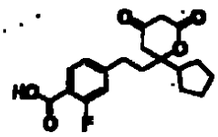
H), 2.40 (m, 5 H), 2.73 (m, 5 H), 3.04 (t, J=12.57 Hz, 2 H), 3.13 (s, 3 H), 7.03 (s, 1 H), 7.52 (d, J=1.52 Hz, 1 H), 7.80 (s, 1 H), 7.90 (d, J=2.58 Hz, 1 H) Anal. Calcd. For $C_{28}H_{31}N_4O_3SF_3$: C, 58.74; H,5.27; N, 9.45. Found: C, 58.50; H, 5.40; N, 9.04.

Example B(6):Methyl 4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-fluorobenzoate



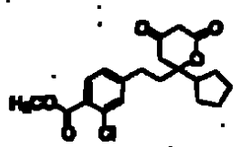
The title compound was prepared analogously to example B(2) where 4-bromo-2-fluoro-benzoic acid methyl ester was substituted in place of . 4-bromo-2-chlorobenzenesulfonyl chloride in step 1 of that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.38-2.30 (m, 11 H), 2.80-3.15 (m, 6 H), 3.88 (s, 3 H), 6.91 (d, J=7.91 Hz, 1 H), 7.17 (m, 1 H), 7.93 (d, J=7.56 Hz, 1 H)

Example B(6): 4-[2-(2-Cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-fluorobenzoic acid



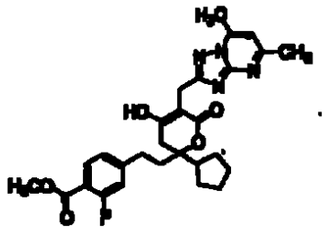
Methyl 4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-fluorobenzoate (example B(5)) (300mg) was treated with 4N NaOH (10ml) and stirred for 4 hrs at room temperature. The mixture was then acidified with 1N HCl (20ml) and the product was extracted with ethyl acetate (2x20ml). The combined organic layers were dried over magnesium sulfate and concentrated to a solid. The solid was recrystallised from diethyl ether to afford the title compound as a white solid (120mg). ^{1}H NMR (300MHz, MeOD): δ 1.38-2.30 (m, 11 H), 2.80-3.12 (m, 6 H), 6.91 (d, J=7.19 Hz, 1 H), 7.17 (m, 1 H), 7.88 (d, J=719 Hz, 1 H)

Example B(7): Methyl 3-chloro-4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]benzoate



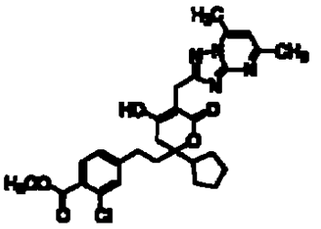
The title compound was prepared analogously to example B(2) where 4-bromo-2-chloro-benzoic acid methyl ester was substituted in place of . 4-bromo-2-chlorobenzenesulfonyl chloride in step 1 of that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.38-2.30 (m, 11 H), 2.78-3.15 (m, 6 H), 3.88 (s, 3 H), 7.10 (s, 1 H), 7.19 (d, J=1,58 Hz, 1 H), 7.62 (d, J=1.58 Hz, 1 H)

Example B(8): Methyl 4-(2-(2-cyclopentyl-5-((5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl)-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-6-yl)ethyl)-3-fluorobenzoate



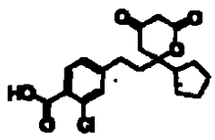
The title compound was prepared analogously to example A(1) where methyl 4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-fluorobenzoate (example B(5)) was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione in that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.25-1.85 (m, 8 H), 2.01-1.10 (m, 3 H), 2.59-2.80 (m, 10 H), 3.10 (t, J=12.57 Hz, 1 H) 3.88 (s, 3 H), 6.91 (d, J=2.57 Hz, 1 H) 6.99 (s, 1 H), 7.15 (d, J=1.58 Hz, 1 H), 7.92 (m, 1 H) Anal. Calcd. For $C_{28}H_{31}N_4O_6F$: C, 64.36; H, 5.98; N, 10.72. Found: C, 64.50; H, 5.40; N, 10.70.

Example B(9): Methyl 2-chloro-4-(2-(2-cyclopentyl-5-((5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl)-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-6-yl)ethyl)benzoate



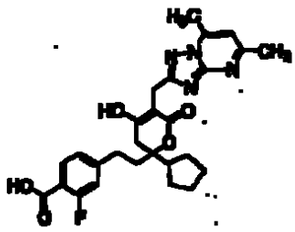
The title compound was prepared analogously to example A(1) where methyl 2-chloro-4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]benzoate (example B(7)) was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione in that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.25-1.85 (m, 8 H), 2.01-1.10 (m, 3 H), 2.59-2.80 (m, 10 H), 3.10 (t, J=12.57 Hz, 1 H) 3.88 (s, 3 H), 6.91 (d, J=2.57 Hz, 1 H) 6.99 (s, 1 H), 7.10 (s, 1 H), 7.19 (d, J=1.8 Hz, 1 H), 7.62 (d, J=1.58 Hz, 1 H)

Example B(10): 2-Chloro-4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]benzoic acid



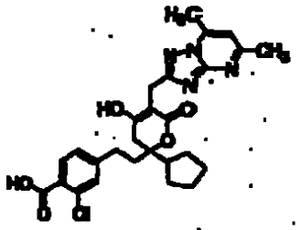
The title compound was prepared analogously to example B(6): where methyl 2-chloro-4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]benzoate (example B(7)) , was substituted in place of methyl 4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-fluorobenzoate in that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.38-2.30 (m, 11 H), 2.78-3.15 (m, 6 H), 7.10 (s, 1 H), 7.19 (d, J=1.58 Hz, 1 H), 7.62 (d, J=1.58 Hz, 1 H) 12.30 (s, 1 H).

Example B(11): 4-(2-[2-Cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-5,6-dihydro-2H-pyran-2-yl]ethyl)-3-fluorobenzoic acid



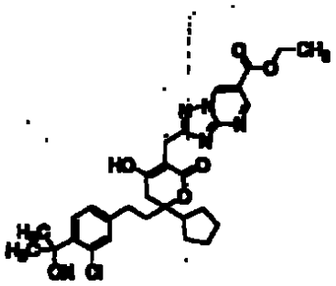
The title compound was prepared analogously to example A(1) where 4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]-2-fluorobenzoic acid (Example B(6): was substituted in place of 6-cyclopentyl-6-[2-(3-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione in that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.25-1.85 (m, 8 H), 2.01-1.10 (m, 3 H), 2.58-2.80 (m, 10 H), 3.10 (t, J=12.57 Hz, 1 H), 6.94 (d, J=2.57 Hz, 1 H) 6.99 (s, 1 H), 7.20 (d, J=8.29 Hz, 1 H), 7.90 (m, 1 H)

Example B(12): 2-Chloro-4-(2-[2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-5,6-dihydro-2H-pyran-2-yl]ethyl)benzoic acid



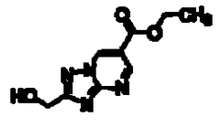
The title compound was prepared analogously to example A(1) where 2-chloro-4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]benzoic acid (example B(10)) was substituted in place of 6-cyclopentyl-6-[2-(3-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione in that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.25-1.85 (m, 8 H), 2.01-1.10 (m, 3 H), 2.58-2.80 (m, 10 H), 3.10 (t, J=12.57 Hz, 1 H), 6.99 (s, 1 H), 7.10 (s, 1 H), 7.22 (d, J=7.26 Hz, 1 H), 7.80 (d, J=7.58 Hz, 1 H)

Example B(13): Ethyl 2-[[6-[2-[3-chloro-4-(1-cyano-1-methylethyl)phenyl]ethyl]-6-cyclopentyl-4-hydroxy-2-oxo-5,6-dihydro-2H-pyran-3-yl]methyl][1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate



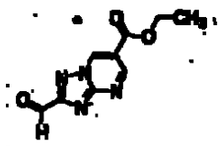
The title compound was prepared analogously to example A(1) where 2-[2-chloro-4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-phenyl]-2-methyl-propionitrile from step 5 of example B(22) was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione and 2-formyl-[1,2,4]triazolo[1,5-]pyrimidine-6-carboxylic acid ethyl ester from step 2 belowwas substituted in place of 2,5-dimethyl-2*H*-[1,2,4]triazole-3-carboxaldehyde in that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.38 (t, *J*=7.68, Hz, 3 H) 1.42-1.66 (m, 8 H), 1.65 (s, 6 H), 2.00-2.25 (m, 5 H), 3.24-3.48 (m, 5 H), 4.24 (q, *J*=12.06 Hz, 2 H), 6.89-7.39 (m, 5 H). Anal. Calcd. For $C_{31}H_{34}ClN_5O_5$: C, 62.89; H, 5.79; N, 11.83. Found: C, 62.94; H, 5.73; N, 11.46.

Step 1: 2-Hydroxymethyl-[1,2,4]triazolo[1,5]pyrimidine-6-carboxylic acid ethyl ester



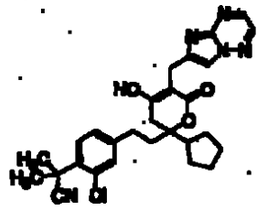
5-Amino-1H-[1,2,4]triazol-3-yl)-methanol (Bru-Magniez et al US (1995) US 5387747 A19950207) (7.9g, 41.6mmol) was mixed with 2-formyl-3-oxo-propionic acid ethyl ester (Toni Sigeri et al Synthesis (1995) 5 pg 400-402), (6.0g, 41.6mmol) in acetic acid (30ml). The reaction mixture was heated to 60°C for 16hrs. After which time the mixture was cooled to room temperature and diluted with diethyl ether (200ml). Product crashes out of solution. The solids are then filtered and washed with diethyl ether (200ml), product dried in vacc oven for 5 hrs. To afford title compound as a white solid (8.0g). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.47 (t, *J*=6.97, Hz, 3 H) 3.00 (bs, 1 H) 4.53 (q, *J*=7.16 Hz, 2 H), 5.00 (s, 2 H) 9.40 (d, *J*=2.07, Hz, 1 H) 9.50 (d, *J*=2.07, Hz, 1 H)

Step 2: 2-Formyl-[1,2,4]triazolo[1,5-]pyrimidine-6-carboxylic acid ethyl ester



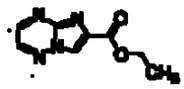
2-Hydroxymethyl-[1,2,4]triazolo[1,5]pyrimidine-6-carboxylic acid ethyl ester (1.0g, 4.6mmol) was mixed with TEMPO (75mg, 7.5% by wt) and $PhI(OAc)_2$ (1.59g, 4.95mmol) in dichloromethane (7.5ml). The reaction was stirred at room temperature for 18hrs after which time the reaction was Purified by flash column chromatography (0% to 100% EtOAc in hexanes) gave the product as a white solid (500mg.). ^1H NMR (300MHz, $CDCl_3$): δ 1.42 (t, J=6.97, Hz, 3 H), 4.48 (q, J=6.97 Hz, 2 H), 8.00 (s, 2 H) 9.39 (d, J=2.26, Hz, 1 H) 10.12 (d, J=2.26, Hz, 1 H), 10.20 (s, 1 H).

Example B(14): 2-(2-Chloro-4-[2-[2-cyclopentyl-4-hydroxy-6-(imidazo[1,2-b][1,2,4]triazin-6-ylmethyl)-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]phenyl)-2-methylpropanenitrile



Prepared analogously to example A(1) substituting imidazo[1,2-b][1,2,4]triazine-6-carbaldehyde (47 mg, 0.34 mmol, from step 2 below) in place of 5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde and 2-[2-chloro-4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-phenyl]-2-methyl-propionitrile (67 mg, 0.22 mmol from step 5 of example B(22)) in place of cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione. Yield: 10 mg, 8.7%. ^1H NMR (400 MHz, $CDCl_3$) δ 1.24-1.74 (m, 8 H), 1.88 (s, 6 H), 1.96-2.02 (m, 2 H), 2.39 (t, J = 8.84 Hz, 1 H), 2.50 (d, J = 17.68 Hz, 1 H), 2.63-2.71 (m, 2 H), 2.76 (d, J = 17.94 Hz, 1 H), 4.02 (d, J = 3.03 Hz, 2 H), 7.06 (dd, J = 8.08, 1.77 Hz, 1 H), 7.20 (d, J = 1.77 Hz, 1 H), 7.34 (d, J = 8.08 Hz, 1 H), 7.89 (s, 1 H), 8.44 (dd, J = 21.73, 2.02 Hz, 2 H).

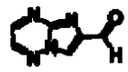
Step 1: Imidazo[1,2-b][1,2,4]triazine-6-carboxylic acid ethyl ester



A solution of 3-amino-1,2,4-triazine (5.0 g, 52 mmol) and ethyl bromopyruvate (11 mL, 88 mmol) in ethanol (50 mL) was heated to reflux for 20 minutes. The reaction was cooled to room temperature, and then partitioned between 200 mL of EtOAc and 200 mL of water. The layers were separated, and the organic layer was dried over $MgSO_4$. The solids were removed by filtration, and then the solvent was removed by rotary evaporation. The residue was purified by

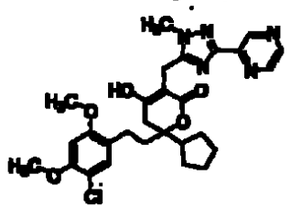
chromatography (90 g SiO_2, 60 to 70% EtOAc in hexanes) to give the desired product (181 mg, 1.8%). MS (ESI): 192.4 $(M+H)^+$.

Step 2: Imidazo[1,2-b][1,2,4]triazine-6-carbaldehyde



To a solution of imidazo[1,2-b][1,2,4]triazine-6-carboxylic acid ethyl ester (500 mg, 2.6 mmol, from step 1 above) in CH_2Cl_2 (15 mL) cooled to –78 °C was added diisobutylaluminum hydride (2.6 mL, 1.5 M in toluene). The reaction was stirred for one hour, and then extra diisobutylaluminum hydride (1 mL, 1.5 M) was added. After 20 more minutes, the cold reaction was quenched with EtOAc (10 mL), and then MeOH (10 mL). After the reaction had warmed to room temperature, 30 mL of 0.3 M HCl was added. The layers were separated. The aqueous phase was extracted three times with 10 mL of CH_2Cl_2. After the organic layers were combined and dried over $MgSO_4$, the solids were removed by filtration. The organic liquid was concentrated by rotary evaporation, and the resulting oil was chromatographed (40 g SiO_2, 50 to 100% EtOAc in hexanes) to give the desired product (47 mg, 12%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 2 H), 8.82 (d, J = 1.77 Hz, 1 H), 10.25 (s, 1 H).

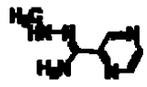
Example 8(18): 6-[2-(5-Chloro-2,4-dimethoxyphenyl)ethyl]-6-cyclopentyl-4-hydroxy-3-[(1-methyl-3-pyrazin-2-yl-1H-1,2,4-triazol-5-yl)methyl]-5,6-dihydro-2H-pyran-2-one



A solution of 6-[2-(5-chloro-2,4-dimethoxy-phenyl)-ethyl]-6-cyclopentyl-dihydro-pyran-2,4-dione (0.300 g, 0.78 mmol, from step 6 below) in hot isopropanol (5 mL) was treated with $(CH_3)_2NHBH_3$ (48 mg, 0.815 mmol, 1.04 equiv), then with a solution of 2-methyl-5-pyrazin-2-yl-2*H*-[1,2,4]triazole-3-carbaldehyde dihydrochloride monohydrate (229 mg, 0.819 mmol, 1.05 equiv, from step 3 below) in isopropanol (3 mL) containing triethylamine (0.230 mL, 2 equiv). The reaction mixture was stirred at room temperature, resulting in complete conversion after 1 h. The mixture was acidified with 1 M aqueous HCl to a pH of 2, stirred for 10 min, and concentrated *in vacuo* to afford a resin. This was diluted with water and extracted with dichloromethane containing 10% methanol (3 x 15 mL). The extract was dried over Na_2SO_4, filtered, and concentrated, affording the crude product (410 mg). This material was recrystallized from hot methylene chloride/ether, then the resulting solid triturated with acetone containing petroleum ether, filtered, and dried, affording the title product (107 mg, 24%). ^1H NMR (300 MHz, DMSO-d_6): δ 1.28-1.75 (m, 8H), 1.78-2.13 (m, 2H), 2.37 (m, 1H), 2.45-2.50 (m, 2H, overlap with DMSO-d_6), 2.65 (d, J = 17.9 Hz, 1H), 2.73

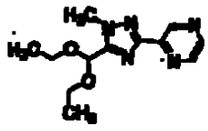
(d, J = 17.9 Hz, 1H), 3.73 (s, m overlap, 5H), 3.80 (s, 3H), 3.95 (s, 3H), 6.69 (s, 1H), 7.05 (s, 1H), 8.6 (m, overlap, 2H), 8.93 (s, 1H), 11.07 (br s, 1H). LC-MS (APCI) calcd for $C_{29}H_{33}ClN_6O_5$: 553.21, found ($M+H^+$): 554.4 m/z.

Step 1: *N*-Methylpyrazine-2-carbohydrazonamide



A 2-L flask was charged with molten 2-cyanopyrazine (50.0 g, 0.48 mol), methylhydrazine (80.0 g, 1.7 mol, 3.6 equiv), and ethanol (300 mL). The mixture was stirred at room temperature under nitrogen for 3 h, upon which time the reaction appeared complete by LC/MS. The yellow needles which had crystallized were filtered and washed with heptane to remove the unreacted methylhydrazine. The filtrate was concentrated *in vacuo* to a small volume, resulting in the formation of additional precipitate. The filtration, washing, and concentration process was repeated three times, affording additional batches of product. The combined batches were suspended in heptane (400 mL), stirred for 1 h, filtered, washed with heptane, and dried *in vacuo* at 50 °C overnight, affording the title amidrazone (55.4 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.01 (s, 3H), 3.80 (br s, 1H), 5.04 (br s, 2H), 8.41 (s, 1H), 8.48 (s, 1H), 9.32 (s, 1H). MS (APCI) calcd for $C_6H_9N_5$: 151.09, found ($M+H^+$): 152.1.

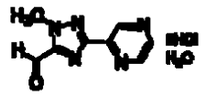
Step 2: 2-(5-Diethoxymethyl-1-methyl-1*H*-[1,2,4]triazol-3-yl)-pyrazine



A 1-L flask was charged with diethoxyacetonitrile (25.0 g, 0.19 mol), a solution of sodium methoxide in methanol (4.32 g of 25 wt% solution, 0.02 mol, 10 mol%), and methanol (200 mL). The mixture was stirred at room temperature for 20 h, affording a solution of the imidate ester, 2,2-diethoxy-acetimidic acid methyl ester. The reaction mixture was treated with the amidrazone, *N*-methylpyrazine-2-carbohydrazonamide (28.7 g, 0.19 mol, 1 equiv), from Step 1, and acetic acid (16.0 g, 0.30 mol, 1.5 equiv). The mixture was stirred at room temperature for 3 h, upon which time the reaction was complete by LC/MS. The volatiles were removed *in vacuo*, affording a viscous oil. This was basified with 20% Na_2CO_3 (100 mL) and saturated $NaHCO_3$ (200 mL), and extracted several times with ether (2 L total). The ether phase was washed with water (1 x 200 mL), dried over Na_2SO_4, filtered, and evaporated, affording the title acetal as a yellow oil (44.8 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, J=6 Hz, 6H), 3.62 (5-line pattern, J=6 Hz, 2H), 3.79 (5-line pattern, J=6 Hz, 2H), 4.08 (s, 3H),

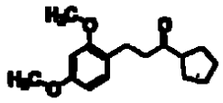
5.68 (s, 1H), 8.56 (m, 1H), 8.63 (m, 1H), 9.94 (s, 1H). MS (APCI) calcd for $C_{11}H_{11}N_5O_2$: 269.14, found ($M+H^+$): 284.1

Step 3: 2-Methyl-5-pyrazin-2-yl-2*H*-[1,2,4]triazole-3-carbaldehyde dihydrochloride monohydrate



The acetal from step 2, 2-[5-(diethoxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl]pyrazine (44.5 g, 0.17 mol) was dissolved in water (150 mL) and conc. HCl (30.0 mL of 12 M, 0.36 mol, ~ 2 equiv). The solution was degassed with nitrogen for 2 min and heated in an oil bath at a bath temperature of 60 °C for 2 h, resulting in complete hydrolysis of the acetal group. The volatiles were removed *in vacuo*, affording a yellow solid (49.8 g). This was suspended in dichloromethane (1 L), refluxed under nitrogen for 1 h, then filtered while still hot. The filter cake was washed with dichloromethane and dried *in vacuo* at 50 °C for 4 h, affording the title product (41.0 g, 81%) as a hygroscopic yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.21 (s, 3H), 8.50 (br s, 4H), 8.75 (m, 2H), 9.27 (s, 1H), 10.01 (s, 1H). MS (APCI) calcd for $C_8H_7N_5O$: 189.07, found ($M+H^+$): 190.1, 208.1 (hydrate); Anal. Calcd. For $C_8H_{11}Cl_2N_5O_2$: C, 34.30; H, 3.96; N, 25.00; O, 11.42; Cl, 25.31. Found: C, 33.43; H, 3.96; N, 24.70; O, 11.17; Cl, 25.44.

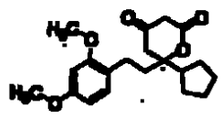
Step 4: 1-Cyclopentyl-3-(2,4-dimethoxy-phenyl)-propan-1-one



A solution of 2,4-dimethoxybenzaldehyde (10.27 g, 45 mmol) and methyl cyclopentyl ketone (6.06 g, 54 mmol) in anhydrous ethanol (81 mL) was treated with 5 M NaOH (aq) (18 mL, 90 mmol) and the mixture stirred at room temperature for 18 h. The volatiles were removed *in vacuo*. The residue was extracted with ether (100 mL) and the extract washed with water (3 x 60 mL), then with brine. The ethereal solution was dried over $MgSO_4$, filtered, and concentrated *in vacuo*, affording the intermediate chalcone in a crude yield of 14.63 g. The crude intermediate (14.52 g) was dissolved in 110 mL ethyl acetate, treated with platinum oxide (5 mole%) and stirred over 1 atm of H_2 at room temperature overnight. The Pt was filtered through a fine fritted funnel and the black residue washed with ethyl acetate. The filtrate was concentrated *in vacuo* to give a yellowish resin. The resin was chromatographed using silica gel and 6:1 hexanes/ethyl acetate, yielding 6.02 g (41%) of the ketone as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.48-1.81 (m, 8H), 2.67 (m, 2H), 2.80 (m, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 6.37

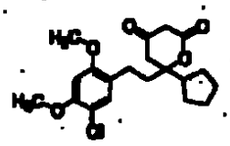
(dd, J=8.1, 2.1 Hz, 1H), 6.41 (d, J=2.1 Hz, 1H), 7.00 (d, J=8.1 Hz, 1H). MS(APCI) calcd for $C_{22}H_{32}O_5$: 392.2; found ($M+H^+$): 393.1.

Step 5: 6-Cyclopentyl-6-[2-(2,4-dimethoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione



Methylacetoacetate (1.63 mL, 15.1 mmol) was dissolved in dry THF (42 mL) and cooled to 0 °C. NaH (60% in mineral oil, 0.604 g, 15.1 mmol) were carefully added and the reaction mixture was stirred for 20 min. A solution of BuLi in hexanes (1.6 M, 9.44 mL, 15.1 mmol) was added dropwise and the resulting mixture was stirred an additional 20 min. A solution of 3-(2,4-dimethoxyphenyl)-1-cyclopentylpropan-1-one (2.33 g, 7.55 mmol) from Step 4 above in THF (37 mL) was added dropwise. After stirring 1 h, the reaction mixture was quenched with saturated aq NH_4Cl (100 mL) and extracted with Et_2O (600 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was then stirred overnight in a mixture of 0.1 M NaOH (370 mL) and THF (37 mL). After the addition of solution of 10% aqueous $KHSO_4$ (50 mL), the resulting mixture was stirred 30 min and then extracted with Et_2O (600 mL). The organic phase was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (50% EtOAc in hexanes) to give the product (1.54 g, 52%) as a white foam: ^1H NMR ($CDCl_3$) δ 1.43 (m, 2 H), 1.76 (m, 8 H), 2.33 (m, 1H), 2.58 (m, 2H), 2.78 (s, 2H), 3.43 (s, 2H), 3.78 (s, 6H), 6.37 (s, 1H), 6.47 (s, 1H), 6.93 (d, J = 7.23 Hz, 1H). MS (APCI) calcd for $C_{22}H_{30}O_5$: 346.2; found (M+1): 347.0.

Step 6. 6-[2-(5-Chloro-2,4-dimethoxy-phenyl)-ethyl]-6-cyclopentyl-dihydro-pyran-2,4-dione

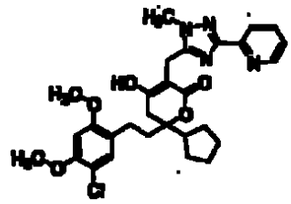


A solution of 6-[2-(2,4-dimethoxyphenyl)ethyl]-6-cyclopentyldihydro-2*H*-pyran-2,4(3*H*)-dione (from Step 5, above) (4.00 g, 13 mmol) in CH_2Cl_2 (20 mL) was cooled to -6 °C and treated with a solution of SO_2Cl_2 (1.94 g, 14.3 mmol) in CH_2Cl_2 (10 mL) dropwise under nitrogen. The reaction mixture was stirred for an additional 15 minutes at -6 °C, then allowed to warm gradually to room temperature. After a total reaction time of 2h, an aqueous solution of $NaHCO_3$ (5 wt%) was added to achieve a pH of 8 in the aqueous phase. The volatiles were removed *in vacuo*. The residue was treated with water and extracted with ethyl acetate (3 x 25 mL). The combined ethyl acetate extract was acidified to a pH 2 using 2 N HCl, then washed

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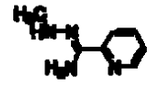
with water. The organic phase was dried over Na_2SO_4, filtered, and concentrated to a yellowish solid. Recrystallization from ether afforded the title product as a white solid (2.18 g, 44%). ^1H NMR ($CDCl_3$) δ 1.74 (m, 6H), 2.22 (m, 1H), 2.58 (m, 2H), 2.78 (s, 2H), 3.43 (s, 2H), 3.82 (s, 3H), 3.92 (s, 3H), 6.44 (s, 1H), 7.07 (s, 1H). HRMS calcd for $C_{22}H_{23}O_5Cl$ ($M+H^+$): 391.1469, found 391.1475.

Example B(16): 6-[2-(5-Chloro-2,4-dimethoxyphenyl)ethyl]-6-cyclopentyl-4-hydroxy-3-[(1-methyl-3-pyridin-2-yl-1H-1,2,4-triazol-5-yl)methyl]-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example B(15) using 2-methyl-5-pyridin-2-yl-2*H*-[1,2,4]triazole-3-carbaldehyde from step 3 below in place of 2-methyl-5-pyrazin-2-yl-2*H*-[1,2,4]triazole-3-carbaldehyde dihydrochloride monohydrate, and omitting the triethylamine. The crude material obtained after the aqueous workup (425 mg) was chromatographed on silica gel using a gradient of ethyl acetate containing 1% methanol to 15% methanol. The product-containing fractions were concentrated and the resulting solid recrystallized from hot dichloromethane/ether, affording 43 mg (10%) of the title product as a hydrated hydrochloride salt. ^1H NMR (300 MHz, DMSO-d_6): δ 1.15-1.8 (m, 8H), 1.8-1.9 (m, 2H), 2.05 (m, 1H), 2.15-2.45 (m, 4H, overlap), 3.6- 3.75 (s, m overlap, 6H), 3.80 (s, 3H), 3.95 (s, 3H), 6.67 (s, 1H), 6.82 (s, 1H), 7.3 (br m, 1H), 7.85 (br m, 2H), 8.62 (br m, 1H). LC-MS (APCI) calcd for $C_{28}H_{32}ClN_4O_5$: 552.21, found ($M+H^+$): 553.4 m/z. Anal. Calcd. For $C_{28}H_{31}Cl_2N_4O_5$: C, 57.33; H, 5.97; N, 9.22; Found: C, 57.48; H, 5.41; N, 9.12.

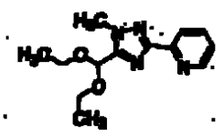
Step 1: *N*'-Methylpyridine-2-carbohydrazonamide



This compound was prepared by a modification of a reported procedure (*J. Het Chem.* 1975, *12*, 855): A 2-L, 3-necked round bottom flask was charged with 2-cyanopyridine (40 g, 0.384 mol), methylhydrazine (93.7 g, 5.3 equiv, 2.035 mol), and ethanol (200 mL). The reaction was stirred under N_2, overnight at room temperature. An additional equiv of hydrazine was added (6.3 equiv cumulative total in reaction mixture) and stirred for an additional 2-3 h at room temperature. The EtOH and excess hydrazine were distilled off *in vacuo* to afford a yellow crystalline solid. The yellow solid was triturated with benzene, affording a slurry of white

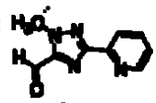
crystals. The crystals were filtered, washed with a minimal amount of benzene and dried overnight in a vacuum oven at 50 °C. The reaction yielded 41.33 g (71.6%) of the product as white crystals. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.97 (s, 3H), 4.02 (br s, 1H), 5.30 (br s, 1H), 7.20 (m, 1H), 7.88 (m, 1H), 8.08 (m, 1H), 8.45 (m, 1H). MS (APCI) calcd for $C_7H_{10}N_4$: 150.09, found (M+H$^+$): 151.3

Step 2: 2-(5-Diethoxymethyl-1-methyl-1*H*-[1,2,4]triazol-3-yl)-pyridine



A 1-L, 3-necked round bottom flask was charged with a solution prepared from sodium methoxide (9.41 g, 0.174 mol, 0.9 equiv) in anhydrous methanol (150 mL). A solution of diethoxyacetonitrile (25 g, 0.193 mol) in anhydrous methanol (70 mL), was added to the methoxide solution, slowly, over 15 min, via an addition funnel. The reaction was then stirred overnight at room temperature, and the excess methanol was evaporated, *in vacuo*. The resulting oil was diluted with water and extracted into ethyl acetate (2 x 200 mL), then CH_2Cl_2 (2 x 200 mL). The organic phases were combined and dried over Na_2SO_4, filtered and concentrated *in vacuo* affording 9 g, (29%) of crude methyl 2,2-diethoxyethanimidoate having a purity of 80-85% by 1H NMR. This was used in the next step without further purification. A 500-mL round bottom flask was charged with a solution of the amidrazone from Step 1, *N*-methylpyridine-2-carbohydrazonamide (22 g, 0.0548 mol) in methanol (75 mL), along with a solution of the crude imidate ester (8.84 g, 0.0548 mol) in methanol (75 mL). The mixture was treated with glacial acetic acid (4.75 mL, 1.5 equiv), and stirred at room temperature overnight while monitoring by LC/MS for disappearance of the amidrazone. The methanol was evaporated *in vacuo*, and the resulting oil was neutralized with saturated, aqueous $NaHCO_3$. The product was extracted into ethyl acetate (3 x 150 mL) and the organic phase dried over Na_2SO_4, filtered and concentrated, to give a yellow oil (11.08 g, 76 % crude yield) of the acetal intermediate that was used in the next step without purification.

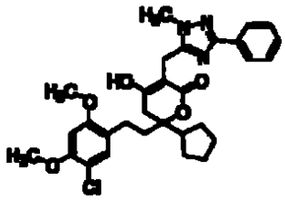
Step 3: 3-Methyl-5-pyridin-2-yl-2*H*-[1,2,4]triazole-3-carbaldehyde



The acetal from step 2, 2-[5-(diethoxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl]pyridine (11.08 g, 0.042 mol) was dissolved in 1.5 equiv of 2 N HCl (aq) and stirred at 40-50 °C, overnight. The mixture was concentrated, yielding a viscous oil, which was then basified to pH 10 using saturated aqueous Na_2CO_3. The mixture was then extracted using ethyl acetate (4 x

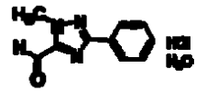
200 mL), the organic layer dried over Na_2SO_4, filtered and concentrated, to a yellow solid. The solid was dissolved in a minimal amount of hot ethyl acetate, scratched and diluted with hexanes to recrystallize the product, affording 3.6 g (45 %) of the desired aldehyde as a yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.26 (s, 3H), 7.46 (m, 1H), 7.82 (m, 1H), 8.15 (m, 1H), 8.78 (m, 1H), 10.08 (s, 1H). MS (APCI) calcd for $C_9H_8N_4O$: 188.07, found ($M+H^+$): 189.3.

Example B(17): 6-[2-(5-Chloro-2,4-dimethoxyphenyl)ethyl]-6-cyclopentyl-4-hydroxy-3-[(1-methyl-3-phenyl-1H-1,2,4-triazol-5-yl)methyl]-5,6-dihydro-2H-pyran-2-one



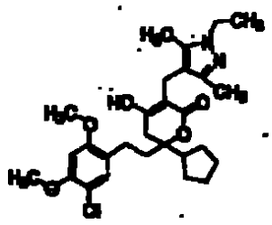
The title compound was prepared analogously to example B(15) using 2-methyl-5-phenyl-2*H*-[1,2,4]triazole-3-carbaldehyde hydrochloride hydrate from step 1 below in place of 2-methyl-5-pyrazin-2-yl-2*H*-[1,2,4]triazole-3-carbaldehyde dihydrochloride monohydrate, and using one equivalent of triethylamine instead of two. Yield: 100 mg (23%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.30-1.77 (m, 8H), 1.86 (m, 1H), 2.1 (m, 1H), 2.35 (m, 1H), 2.45-2.55 (m, 2H, overlap with DMSO-d_6), 2.68 (d, *J*=17.6 Hz, 1H), 2.73 (d, *J*=17.6 Hz, 1H), 3.55-3.7 (s, overlap with ABQ, *J*=16.7 Hz, total 5H), 3.82 (s, 3H), 3.86 (s, 3H), 6.65 (s, 1H), 7.12 (s, 1H), 7.29 (m, 3H), 7.71 (d, J=6 Hz, 2H). 10.96 (br s, 1H). LC-MS (APCI) calcd for $C_{29}H_{33}ClN_3O_5$: 551.22, found ($M+H^+$): 552.4 m/z.

Step 1: 2-Methyl-5-phenyl-2*H*-[1,2,4]triazole-3-carbaldehyde hydrochloride hydrate



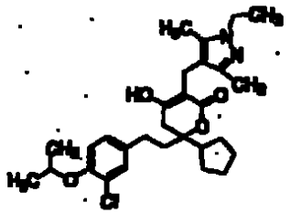
The title compound was prepared analogously to step 3 of example B(15): using *N*-methylbenzene-carbohydrazonamide (the free base of the amidrazone reported in: Metz, H.I.; Neunhoeffer, H. *Chem. Ber.* 1982, *115*, 2907) in place of *N*-methylpyrazine-2-carbohydrazonamide in step 3 of that example. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.17 (s, 3H), 7.30 (br m, 3H), 7.49 (m, 3H), 8.02 (d, *J*=9 Hz, 2H), 9.99 (s, 1H). MS (APCI) calcd for $C_{10}H_9N_3O$: 187.07, found ($M+H^+$): 188.3.

Example B(18): 6-[2-(5-Chloro-2,4-dimethoxyphenyl)ethyl]-6-cyclopentyl-3-[(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example B(15) using 1-ethyl-3,5-dimethyl-*1H*-pyrazole-4-carbaldehyde in place of 2-methyl-5-pyrazin-2-yl-2*H*-[1,2,4]triazole-3-carbaldehyde dihydrochloride monohydrate, and omitting the triethylamine. Following the aqueous workup, the product was recrystallized from a mixture of hot ethyl acetate, methanol and ether, affording 242 mg (80%) of the title product. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 (t, *J*=7 Hz, 3H), 1.23-1.8 (m, overlap, 10H), 2.01 (s, 3H), 2.10 (s, 3H), 2.23 (m, 1H), 2.39 (m, 2H), 2.5 (d, 1H, overlap with DMSO-d_6 peak), 2.67 (d, *J*=17.9 Hz, 1H), 3.15 (ABQ, *J*=15.2 Hz, 2H), 3.74 (s, 3H), 3.82 (s, q overlap, total 5H), 6.7 (s, 1H), 7.0 (s, 1H), 10.56 (br s, 1H). LC-MS (APCI) calcd for $C_{28}H_{37}ClN_2O_5$: 516.24, found (M+H$^+$): 517.4 m/z.

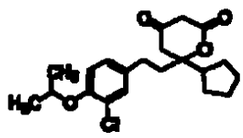
Example B(19): 6-[2-(3-chloro-4-isopropoxyphenyl)ethyl]-6-cyclopentyl-3-[(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



A solution of 6-[2-(3-chloro-4-isopropoxy-phenyl)-ethyl]-6-cyclopentyl-dihydro-pyran-2,4-dione (379 mg; 1.0 mmol from step 1 below) and 1-ethyl-3,5-dimethyl-*1H*-pyrazole-4-carbaldehyde (152 mg; 1.1 mmol) in methanol was heated at 40 °C overnight. The reaction mixture was treated with $(CH_3)_3N{\cdot}BH_3$ (95 mg, 1.1 equiv), and heated at 40 °C overnight again. The reaction was partitioned between EtOAc and H_2O. The EtOAc layer was dried with Na_2SO_4, concentrated, and purified by reverse phase HPLC using 0.1%HOAc in H_2O and CH_3CN. (Column: Water's Bondapak, C18, particle size: 37-55 micron column size: 47x300mm; Flow rate: 70ml/min; Detector: was set at 254 nm; Buffer A: 0.1%HOAc in H_2O; Buffer B: 0.1%HOAc in CH_3CN. The column was equilibrated in A for 20 minutes. The sample was dissolved in 5 ml of DMSO, filtered, and injected onto the column. The gradient was held at 75%A/25% for 5 minutes and then increased linearly to 55%A/45%B in 15 minutes and then continued isocratically at 45%B for another 25 minutes. The desired product eluted at 28 minutes.) The product-containing fractions were lyophilized to afford the title compound as a

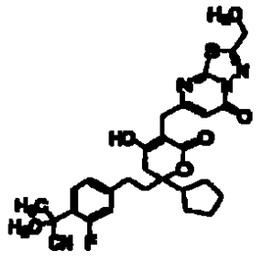
powder (196.2 mg, 40%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.13 (t, 3H), 1.26 (d, m overlap, 6H), 1.35-1.69 (m, 6H), 1.75 (m, 2H), 2.02 (s, 3H), 2.10 (s, 3H), 2.21 (m, 1H), 2.39 (m, overlap, 3H), 2.61 (d, J=16.4 Hz, 1H), 3.1 (m, 2H, overlap with H_2O peak), 3.61 (q, 2H), 4.56 (7 line pattern, 1H), 6.90 (d, J=8.8 Hz, 1H), 7.00 (d, J=8.8 Hz, 1H), 7.11 (s, 1H). LC-MS (APCI) calcd for $C_{28}H_{35}ClN_2O_4$: 514.23, found ($M+H^+$): 515.3 m/z.

Step 1: 6-[2-(3-Chloro-4-isopropoxy-phenyl)-ethyl]-6-cyclopentyl-dihydro-pyran-2,4-dione



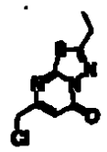
The title compound was prepared analogously to example B(2) where 4-bromo-2-chloro-1-isopropoxy-benzene was substituted in place of 4-bromo-2-chloro-1-methanesulfonyl-benzene in step 2 of that example. ^{1}H NMR ($CDCl_3$): δ 1.38 (d, J = 6.0 Hz, 6H), 1.52-1.82 (brm, 8H), 1.94 (m, 2H), 2.27 (m, 1H), 2.60 (t, J = 7.9 Hz, 2H), 2.78 (s, 2H), 3.43 (s, 2H), 4.50 (m, 1H), 6.88 (d, J = 8.5 Hz, 1H), 6.94 (d, J = 8.5 Hz, 1H), 7.14 (s, 1H) (m, 3H). Anal. Calcd. For $C_{21}H_{27}ClO_4$: C, 66.57; H, 7.18. Found: C, 66.33; H, 6.96.

Example B(20): 2-[4-(3-[2-Cyclopentyl-6-[(2-ethyl-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile



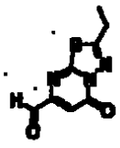
The title compound was prepared on a 0.5-mmol scale analogously to example B(19): except using 2-(4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl)-2-methyl-propionitrile from step 3 of example A(84) in place of 6-[2-(3-chloro-4-isopropoxy-phenyl)-ethyl]-6-cyclopentyl-dihydro-pyran-2,4-dione and 2-ethyl-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-7-carbaldehyde from step 2 below in place of 1-ethyl-3,5-dimethyl-1H-pyrazole-4-carbaldehyde. Yield: 10 mg (4%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.29 (t, 3H), 1.35-1.7 (s, m overlap, 14H), 1.89 (m, 2H), 2.38 (m, 1H), 2.63 (m, overlap, 3H), 2.75 (d, 1H), 3.09 (q, 2H), 3.48 (ABq, 2H), 6.06 (s, 1H), 7.10 (m, overlap, 2H), 7.35 (m, 1H), 10.98 (s, 1H). LC-MS (APCI) calcd for $C_{32}H_{39}FN_4O_4S$: 594.22, found ($M+H^+$): 595.2 m/z.

Step 1: 7-Chloromethyl-2-ethyl-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



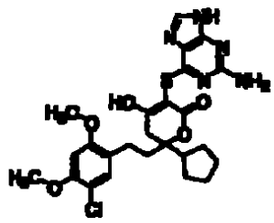
The title compound was prepared by a modification of a procedure described for analogs: (*J. Heterocyclic Chem.* 1993, 20, 1053). A 3-necked, 3-L flask with overhead stirring was charged with warm polyphosphoric acid (approx 250 g), 2-amino-5-ethyl-1,2,4-thiadiazole (45.2 g, 0.35 mol), and ethyl-4-chloroacetoacetate (86.4 g, 0.525 mol, 1.5 equiv). The mixture was heated to 110 °C with vigorous stirring. After 30 minutes, at exothermic reaction took place, resulting in an increase in the temperature to 140 °C, an increase in the viscosity, and the appearance of a darker color. Heating was stopped, the reaction mixture cooled to 80 °C, then treated slowly with water (300 mL) via an addition funnel. The resulting mixture was transferred to a 3-L beaker, cooled in an ice bath, and neutralized to pH 6 to 7 using aqueous NaOH (10%). The solid that precipitated was filtered, washed with water, ether, and petroleum ether, then dried *in vacuo*, affording 68.4 g (83%) of the title product as a sandy-colored crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (t, J=7.5 Hz, 3H), 3.09 (q, J=7.5 Hz, 2H), 4.42 (s, 2H), 6.61 (s, 1H). MS (APCI) calcd for $C_9H_9ClN_3OS$: 229.01, found ($M+H^+$): 230.0.

Step 2: 2-Ethyl-5-oxo-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-7-carboxaldehyde



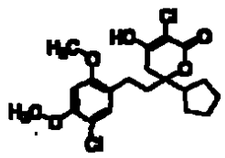
A mixture of 7-Chloromethyl-2-ethyl-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one (11.49 g, 50 mmol), sodium iodide (15 g, 100 mmol, 2 equiv), sodium bicarbonate (12.6 g, 150 mmol, 3 equiv), water (25 mL) and DMSO (250 mL) was stirred and heated at 80 °C for 16 h. The volatiles were mostly removed on the rotary evaporator, then the residue treated with ethyl acetate to precipitate the salts, and the mixture filtered. The filtrate was lyophilized and chromatographed on silica gel using a gradient of ethyl acetate to 3% methanol in ethyl acetate, affording 2-ethyl-7-hydroxymethyl-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one (4.24 g, 40%). This alcohol was dissolved in acetone (150 mL) and refluxed for 3 days with a total of 15 equivalents of MnO_2, added in 3-equiv portions over this time, affording complete conversion to the corresponding aldehyde. The reaction mixture was filtered through celite, the cake washed with acetone (3 x 100 mL), and the filtrate concentrated *in vacuo*, affording the title product (2.84 g, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (t, 3H), 3.10 (q, 2H), 6.96 (s, 1H), 9.90 (s, 1H). MS (APCI) calcd for $C_9H_7ClN_4O_2S$: 209.03, found ($M+H^+$): 210.2.

Example B(21): 3-[(2-Amino-7H-purin-6-yl)thio]-6-[2-(5-chloro-2,4-dimethoxyphenyl)ethyl]-6-cyclopentyldihydro-2H-pyran-2,4(3H)-dione



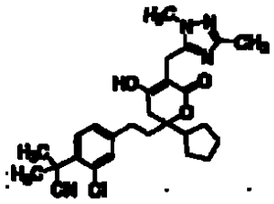
A mixture of 3-chloro-6-[2-(5-chloro-2,4-dimethoxy-phenyl)-ethyl]-6-cyclopentyl-4-hydroxy-5,6-dihydro-pyran-2-one (190 mg, 0.46 mmol, from step 1 below), 2-amino-6H-purine-6-thiol (90 mg, 0.5 mmol) and triethylamine (1 equiv) in DMF (3 mL) was heated at 80 °C overnight. The reaction mixture was partioned between water and ethyl acetate. The organic phase was concentrated, and the product was isolated by reverse-phase HPLC, affording 38 mg (14%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.35-1.75 (m, 8H), 2.0 (m, 1H), 2.18 (m, 1H), 2.35-2.55 (m, 3H, overlap with DMSO-d_6), 2.73 (d, J=17.3 Hz, 1H), 2.88 (d, J=17.3 Hz, 1H), 3.77 (s, 3H), 3.85 (s, 3H), 5.75 (br s, 2H), 6.71 (s, 1H), 7.15 (s, 1H), 7.81 (s, 1H); LC-MS (APCI) calcd for $C_{23}H_{28}ClN_5O_5S$: 545.15, found ($M+H^+$): 546.1 m/z.

Step 1. 3-Chloro-6-[2-(5-chloro-2,4-dimethoxy-phenyl)-ethyl]-6-cyclopentyl-4-hydroxy-5,6-dihydro-pyran-2-one



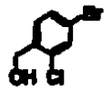
The title compound was prepared by chlorination of 6-[2-(5-chloro-2,4-dimethoxy-phenyl)-ethyl]-6-cyclopentyl-dihydro-pyran-2,4-dione from step 6 of example B(15) with sulfuryl chloride in dichloromethane at room temperature. ^{1}H NMR ($CDCl_3$) δ 1.51 (m, 6H), 1.79 (m, 1H), 2.08, (m, 2H), 2.45 (m, 2H), 2.60 (m, 1H), 2.67 (d, J=17.75, 1H), 2.92 (d, J=17.75, 1H), 3.82 (s, 3H), 3.92 (s, 3H), 6.44 (s, 1H), 7.08 (s, 1H). HRMS calcd for $C_{20}H_{24}O_5Cl_2$ ($M+H^+$) 415.1079, found 415.1083.

Example B(22): 2-[2-Chloro-4-(2-(2-cyclopentyl-6-[(1,3-dimethyl-1H-1,2,4-triazol-5-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)phenyl]-2-methylpropanenitrile



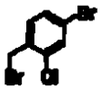
The title compound was prepared analogously to example A(1): where 2-[2-chloro-4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-phenyl]-2-methyl-propionitrile from step 5 below, was substituted in place of 6-[2-(3-chloro-5-ethyl-4-methoxy-phenyl)-ethyl]-6-cyclopentyl-dihydro-pyran-2,4-dione and 2,5-dimethyl-2*H*-[1,2,4]triazole-3-carbaldehyde was substituted instead of 5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde in that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.47-1.74 (m, 8 H), 1.79 (s, 6 H), 2.01-2.11 (m, 5 H), 2.36-2.42 (m, 1 H), 2.58 (d, *J* = 16 Hz, 1 H), 2.80-2.88 (m, 2 H), 2.77 (d, *J* = 16 Hz, 1 H), 3.53 (d, *J* = 16 Hz, 1 H), 3.82 (d, *J* = 16 Hz, 1 H), 7.25 (dd, *J* = 8.2, 1.8 Hz, 1 H), 7.4 (d, *J* = 1.8 Hz, 1 H), 7.45 (d, *J* = 8.2 Hz, 1 H). Anal. Calcd. For $C_{25}H_{32}ClN_3O_3 \cdot 0.25\ H_2O$: C, 64.66; H, 6.73; N, 11.17. Found: C, 64.68; H, 6.74; N, 10.86. ESIMS (MH+): 458.

Step 1: (4-Bromo-2-chloro-phenyl)-methanol



4-Bromo-2-chlorobenzoic acid (5 g, 21.23 mmol) was dissolved in dry THF (100 mL) and cooled to 0 °C. A 1M solution of BH_3.THF in THF (31.85 mL, 31.85 mmol) was slowly added. The reaction was stirred overnight, allowing it to gradually reach room temperature. K_2CO_3 solid (1g) and H_2O (100 mL) were added and the reaction was stirred for 30 minutes. THF was evaporated and residue extracted with EtOAc (30 mL). The organic phase was washed with 1N.HCl (3 x 50 mL), brine (3 x 50 mL), dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (30% EtOAc in hexanes) to give the product (2.80 g, 60%) as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$): δ 4.73 (d, *J* = 6.6 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.42 (dd, *J* = 8.1 Hz, 1.7), 7.62 (d, *J* = 1.7 Hz, 1H)

Step 2: 4-Bromo-1-bromomethyl-2-chloro-benzene

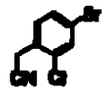


To a magnetically stirring solution of (4-bromo-2-chloro-phenyl)-methanol (2.80g, 12.67 mmol) from step 1 above in CH_2Cl_2 (60.0 mL) under argon at 0 °C, was added carbon tetrabromide (4.41 g, 13.30 mmol) followed by triphenylphosphine (3.48 g, 13.30 mmol). The

250
251

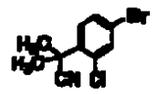
resulting mixture was stirred for 4 hours at room temperature. The resulting reaction mixture was concentrated in vacuo and the crude residue was purified by flash column chromatography (10% EtOAc in Hexanes) to yield the intermediate bromide as a clear oil (3.59 g, 100%). ^{1}H NMR (400MHz, $CDCl_3$): δ 4.53 (s, 2H), 7.29 (d, J = 8.2 Hz, 1H), 7.39 (dd, J = 8.2, 1.9 Hz, 1 H), 7.56 (d, J = 1.9 Hz, 1H).

Step 3: (4-Bromo-2-chloro-phenyl)-acetonitrile



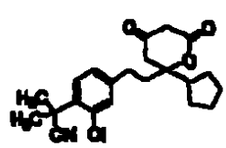
To a magnetically stirring solution of 4-bromo-1-bromomethyl-2-chloro-benzene (3.59g, 12.57 mmol) from step 2 above and tetrabutylammonium bromide (0.41g, 1.27 mmol) in CH_2Cl_2/H_2O 1:1 (50.0 mL), was added a solution of KCN (2.46g, 38.01 mmol) in H_2O (30 mL). The resulting orange mixture was stirred at room temperature for 3 hours. The layers of the resulting reaction mixture were separated and the organic layer was washed with $NaHCO_3$ sat solution (3 x 50 mL), then dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (30% EtOAc in Hexanes) to yield the intermediate as a clear oil (3.59 g, 100%). ^{1}H NMR (400MHz, $CDCl_3$): δ 3.79 (s, 2H), 7.37-7.60 (m, 3H).

Step 4: 2-(4-Bromo-2-chloro-phenyl)-2-methyl-propionitrile



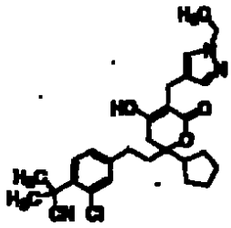
NaH (95%, 1.18 g, 49.35 mmol) was suspended in DMF (25mL) and cooled to 0 °C. 4-bromo-2-chloro-phenyl)-acetonitrile (2.27 g, 9.87 mmol) from step 3 above, was dissolved in THF (10 mL) and slowly added via cannula and the reaction mixture stirred 20 min. MeI (6.10 mL, 98 mmol) was added and the resulting mixture was stirred overnight at room temperature. Reaction was quenched with H_2O (50 mL). Solvents were removed in vacuo and residue partitioned between EtOAc and 1N HCl (50 mL). The organic phase was dried over Na_2SO_4 and evaporated. The crude organic product was purified by flash column chromatography (5% EtOAc in hexanes) to give the product (2.23 g, 87%) as a clear oil. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.34 (d, J = 8.4 Hz, 1H), 7.43 (dd, J = 8.4, 2.0 Hz, 1H), 7.61 (d, J = 1.8 Hz, 1H).

Step 5: 2-[2-Chloro-4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-phenyl]-2-methyl-propionitrile.



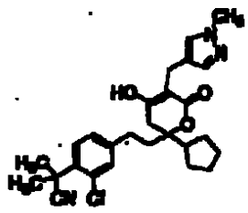
The title compound was prepared analogously to example A(1) where 2-(4-bromo-2-chloro-phenyl)-2-methyl-propionitrile from step 4 above was substituted in place of 1-benzyloxy-2-ethyl-4-iodo-5-propoxy-benzene in step 4 of that example. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.39-1.71 (m, 8H), 1.81-1.87 (m, 8H), 2.10-2.15 (m, 1H), 2.59-2.68 (m, 2H), 3.51 (s, 2H), 3.75 (s, 2H), 7.11 (dd, J = 8.1 Hz, 1.8), 7.27 (d, J = 1.8 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H). MS (ESI): 368 $(M+H)^+$.

Example B(23): 2-[2-Chloro-4-(2-[2-cyclopentyl-5-[(1-ethyl-1H-pyrazol-4-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)phenyl]-2-methylpropanenitrile



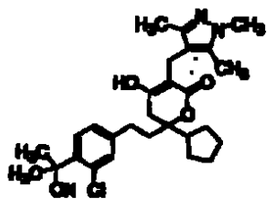
The title compound was prepared analogously to example B(22) where 1-ethyl-1*H*-pyrazole-4-carbaldehyde was substituted instead of 2,5-dimethyl-2*H*-[1,2,4]triazole-3-carbaldehyde in that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.43 (t, J = 7.2 Hz, 3 H), 1.4-1.76 (m, 8 H), 1.76 (s, 6 H), 2.04-2.28 (m, 4 H), 2.63-2.85 (m, 2 H), 3.64-3.74 (m, 3H), 4.06-4.08 (m, 2 H), 6.91-7.8 (m, 5 H), 8.90 (s, 1 H). Anal. Calcd. For $C_{28}H_{33}ClN_2O_3$·0.25 H_2O: C, 67.19; H, 6.95; N, 5.39. Found: C, 67.30; H, 6.99; N, 5.50. ESIMS (M+H+): 497.

Example B(24): 2-[2-Chloro-4-(2-[2-cyclopentyl-4-hydroxy-5-[(1-methyl-1H-pyrazol-4-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)phenyl]-2-methylpropanenitrile



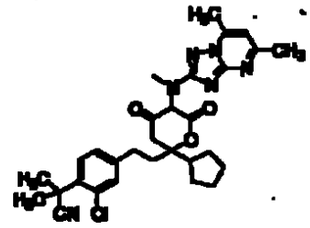
The title compound was prepared analogously to example B(22) where 1-methyl-1*H*-pyrazole-4-carbaldehyde was substituted instead of 2,5-dimethyl-2*H*-[1,2,4]triazole-3-carbaldehyde in that example. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.42-1.69 (m, 8 H), 1.85 (s, 6 H), 2.29-2.79 (m, 5 H), 3.24-3.46 (m, 3 H), 3.81 (s, 2 H), 3.82 (s, 2 H), 6.89-7.39 (m, 5 H), 7.33-7.45 (m, 1 H). Anal. Calcd. For $C_{27}H_{33}ClN_2O_3$·0.5 H_2O: C, 66.04; H, 6.77; N, 5.59. Found: C, 65.94; H, 6.73; N, 5.46. ESIMS (M+H+): 483.

Example B(25): 2-[2-Chloro-4-(2-[2-cyclopentyl-4-hydroxy-6-oxo-5-[(1,3,5-trimethyl-1H-pyrazol-4-yl)methyl]-3,6-dihydro-2H-pyran-2-yl]ethyl)phenyl]-2-methylpropanenitrile



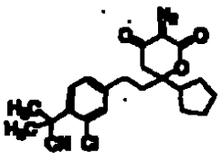
The title compound was prepared analogously to example B(22) where 1,3,5-trimethyl-1*H*-pyrazole-4-carbaldehyde was substituted instead of 2,5-dimethyl-2*H*-[1,2,4]triazole-3-carbaldehyde in that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.40-1.57 (m, 6 H), 1.75 (s, 6 H), 1.70-1.83 (m, 2 H), 1.99 (s, 3 H), 2.08 (s, 3 H), 2.21-2.25 (m, 1 H), 2.49-2.52 (m, 3 H), 2.84 (d, *J* = 16 Hz, 1 H), 3.06 (d, *J* = 14 Hz, 1 H), 3.20 (d, *J* = 14 Hz, 1 H), 3.50 (s, 3 H), 7.06 (dd, *J* =8.2, 1.8 Hz, 1 H), 7.27 (d, *J* = 1.8 Hz, 1 H), 7.39 (d, *J* =8.2Hz 1 H), 10.7 (s, 1 H). Anal. Calcd. For $C_{28}H_{32}ClN_5O_3$.0.25 H_2O: C, 67.69; H, 7.16; N, 8.17. Found: C, 67.72; H, 7.11; N, 8.02. ESIMS (M+H+): 511.

Example B(23): 2-[2-Chloro-4-(2-(2-cyclopentyl-5-[[5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl](methyl)amino]-4,6-dioxotetrahydro-2H-pyran-6-yl)ethyl)phenyl]-2-methylpropanenitrile



A stirred suspension 2-[2-chloro-4-[2-(2-cyclopentyl-5-imino-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-phenyl]-2-methyl-propionitrile (0.63g, 1.53 mmol, from step 1 below), *N*-methyl-4*H*-1,2,4-triazole-3,5-diamine (0.27g, 1.53 mmol, from step 3 below), and $Rh_2(OAC)_2$ (0.00041g, 0.00092 mmol), in hexafluorobenzene (7mL) under argon was heated at 80 °C for 8 hours. The reaction was poured into water (10 mL) and extracted with EtOAc (3 x 5 mL). The organic layers were combined washed with saturated NaCl and dried over Na_2SO_4. The solvents were removed and the residue was purified by flash column chromatography (30-80% % EtOAc in hexanes, then 2-4 % MeOH/CH_2Cl_2) to give the product as a yellow solid (0.056 g, 6%). ^{1}H NMR (300MHz, DMSO-d_6): δ 1.37-2.01 (m, 16 H), 2.26-2.33 (m, 1H), 2.41-2.69 (m, 8H), 3.32 (s, 2H), 3.43 (d, *J* = 2.5 Hz, 3 H), 5.28-5.39 (m, 1H), 7.20-7.21 (m, 1H), 7.29-7.32 (m, 1H), 7.42-7.47 (m, 2H). ESIMS (M+H+): 563.

Step 1: 2-[2-Chloro-4-[2-(2-cyclopentyl-5-imino-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-phenyl]-2-methyl-propionitrile.



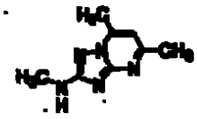
To a stirred solution of 2-[2-chloro-4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-phenyl]-2-methyl-propionitrile (0.5g, 1.29 mmol) from step 5 of example B(22) , and p-acetamidobenzenesulfonyl azide (0.46g, 1.94 mmol) in THF (4mL) under argon was added TEA (0.54 mL, 3.87 mmol). The resulting solution was stirred at 25 °C overnight. The solvents were removed and the residue was purified by flash column chromatography (25-60% % EtOAc in hexanes) to give the product as a yellow oil. ESIMS (MH+): 414.

Step 2: *N*-methyl-4*H*-1,2,4-triazole-3,5-diamine



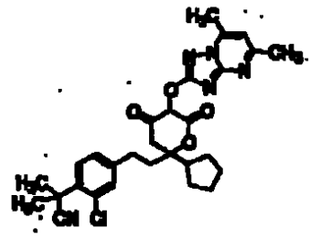
A mixture of N-cyano-N',S-dimethylisothiourea (100 g, 0.77 mol) and 85% hydrazine hydrate (91.2 g, 1.55 mol) in EtOH (350 mL) was refluxed for 2 hours. During the reaction, methanethiol was liberated. Once the reaction was complete (monitored by TLC: CH_2Cl_2 / MeOH = 20/1), the reaction mixture was evaporated to dryness. Petroleum ether was added, and the solid was filtered and washed with petroleum ether to give the product as a pink solid (77 g, 85%). ^{1}H NMR (300MHz, DMSO-d_6): δ 2.59 (s, 3 H), 4.52-6.20 (br m, 3 H), 10.67 (s, 1 H).

Step 3: *N*-methyl-4*H*-1,2,4-triazole-3,5-diamine



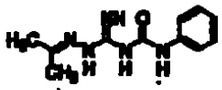
To a solution of *N*-methyl-4*H*-1,2,4-triazole-3,5-diamine (75 g, 0.66 mol, from step 2) in glacial acetic acid (375 mL) was added pentane 2,4-dione (66 g, 0.66 mol), and the mixture was refluxed for 8 hours. The reaction mixture was concentrated under reduced pressure. The residue was taken up into CH_2Cl_2 (1000 mL). The solution was washed with dilute aqueous sodium hydroxide and water. The combined aqueous layers were extracted with CH_2Cl_2 (1000 mL). The combined organic phases were dried over Na_2SO_4. Removal of CH_2Cl_2 under reduced pressure, a yellow precipitate was filtered and washed with petroleum ether to give the product (84 g, 55 %). ^{1}H NMR (300MHz, DMSO-d_6): δ 2.43 (s, 3 H), 2.56 (s, 3 H), 2.80 (s, 3 H), 6.64 (s, 1 H), 8.80 (s, 1 H).

Example B(27): 2-[2-Chloro-4-(2-[2-cyclopentyl-6-[[3,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]oxy]-4,6-dioxotetrahydro-2H-pyran-2-yl]ethyl]phenyl]-2-methylpropanenitrile



The title compound was prepared analogously to example B(28) where 5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ol from step 3 below was substituted instead of (5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-methyl-amine in that example. ^{1}H NMR (300MHz, DMSO-d_6): δ 1.61-1.84 (m, 10 H), 1.88 (s, 6H), 2.12-2.18 (m, 1H), 2.41-2.76 (m, 8H), 3.43 (s, 2H), 3.25-5.30 (m, 1H), 6.53-6.54 (m, 1H), 7.4-7.54 (m, 1H), 7.55-7.57 (m, 1H), 7.68 (s, 1H). ESIMS (MH+): 551.

Step 1: *N*-(Anilinocarbonyl)-3-(1-methylethylidene)hydrazinecarboximidamide



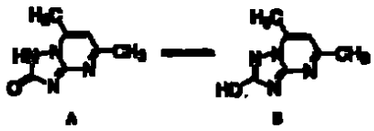
To a suspension of sodium (19 g, 0.82 mol) in acetone (1000 mL) and was added aminoguanidine hydrochloride (100 g, 0.91 mol) in portions. The mixture was refluxed for 60 minutes. The heating bath was removed, and phenyl isocyanate (78.4 g, 0.65 mol) was added dropwise during 30 minutes. The mixture was refluxed for another 30 minutes. The mixture was poured into ice water (2.5 L). The oil solidified at room temperature during an overnight stirring. The solid was filtered and washed with petroleum ether to afford the product as a yellow solid (150 g, 70 %).

Step 2: 5-Amino-2,4-dihydro-3*H*-1,2,4-triazol-3-one



A solution of *N*-(anilinocarbonyl)-2-(1-methylethylidene)hydrazinecarboximidamide (150 g, 0.64 mol) in 2 N hydrochloric acid (200 mL) was refluxed for 30 minutes. The solution was made to pH = 9 by 1 N aqueous sodium hydroxide. The mixture was concentrated until a precipitate was formed. The resultant mixture was cooled to room temperature and kept in the refrigerator over night. The precipitate was filtered to give the product (29 g, 45 %).

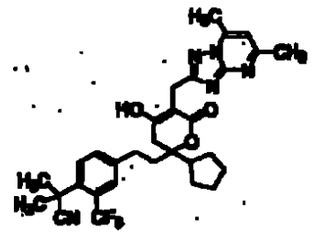
Step 3: 5,7-Dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-ol



A B

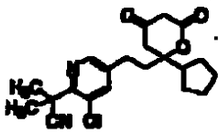
To a solution of 5-amino-2,4-dihydro-3*H*-1,2,4-triazol-3-one (29 g, 0.29 mol) in glacial acetic acid (140 mL) was added pentane2,4-dione (29 g, 0.29 mol) and the solution was refluxed for 8 hours. The reaction mixture was concentrated under reduced pressure to afford a yellow solid. The solid was filtered and washed with ethanol (200 mL) to give the product (42 g, 80%).

Example B(26): 2-[4-[2-[3-Cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-5,6-dihydro-2*H*-pyran-2-yl]ethyl]-3-(trifluoromethyl)phenyl]-2-methylpropanenitrile



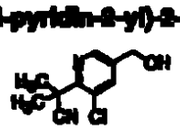
The title compound was prepared analogously to example A(1) where 2-[4-[2-(3-cyclopentyl-4,6-dioxotetrahydro-2*H*-pyran-2-yl)ethyl]-2-(trifluoromethyl)phenyl]-2-methylpropanenitrile (example A(141))) was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione in that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.44-1.76 (br m, 8 H), 1.87 (s, 6 H), 2.23 (m, 2 H), 2.46-2.61 (m, 8 H), 2.80 (m, 3 H), 3.76 (d, *J*=16.2 Hz, 1 H), 3.89 (d, *J*=16.2 Hz, 1 H), 7.10 (s, 1 H), 7.72 (s, 1 H), 7.77 (m, 2 H), 11.01 (s, 1 H). MS (ESI): 592.20 $(M+H)^+$

Example B(28): 2-[3-Chloro-5-[2-(3-cyclopentyl-4,6-dioxotetrahydro-2*H*-pyran-2-yl)ethyl]pyridin-2-yl]-2-methylpropanenitrile



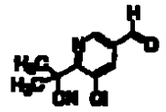
The title compound was prepared analogously to example B(2)where 2-[3-Chloro-5-(3-cyclopentyl-3-oxo-propyl)-pyridin-2-yl]-2-methyl-propionitrile, from step 7, below, was substituted in place of 3-(3-chloro-5-methanesulfonyl-phenyl)-1-cyclopentyl-propan-1-one of that example. ^{1}H NMR ($CDCl_3$) δ: 1.43-1.79 (m, 8 H), 1.84 (s, 6 H), 1.93-1.98 (m, 2 H), 2.25-2.30 (m, 1 H), 2.69-2.84 (m, 4 H), 3.39-3.59 (m, 2 H), 7.55 (s, 1 H), 8.29 (s, 1 H).

Step 1: 2-(3-Chloro-5-hydroxymethyl-pyridin-2-yl)-2-methyl-propionitrile



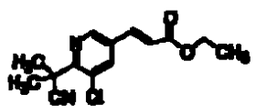
To a magnetically stirring solution of 5,6 dichloronicotinic acid (2.7 g, 14.08 mmol) in THF (70.0 mL), was added isobutyronitrile (6.37 mL, 69.66 mmol) followed by potassium hexamethyldisilazide 0.5 M in toluene (70 mL). The resulting orange mixture was stirred at 60 °C overnight. Solvents were removed and residue portioned between ethyl acetate (100 mL) and 1N HCl (100 mL). The layers of the resulting reaction mixture were separated and the aqueous layer was extracted three additional times with ethyl acetate. The organic layers were combined and dried over Na_2SO_4, filtered and concentrated in vacuo to a yellow solid (3.34 g). This crude residue was dissolved in THF (50 mL) and reaction cooled to 0 °C. BH_3.THF 1M solution in THF (22.50 mL) was added and reaction stirred at 0 °C for 4 hours, then room temperature overnight. Solid K_2CO_3 (2 g) and water (100 mL) were added and the aqueous layer was extracted three additional times with ethyl acetate. The organics were combined dried over Na_2SO_4, filtered and concentrated in vacuo to a clear oil which was purified by silica gel chromatography (hexanes) to give the title compound as a white solid (0.95g, 32%). ESMS (MH+): 210.

Step 2: 2-(3-Chloro-5-formyl-pyridin-2-yl)-2-methyl-propionitrile



A solution of oxalyl chloride (0.45 mL, 5.21 mmol) and in dry CH_2Cl_2 (11 mL), was cooled to -60 °C. Dimethyl sulfoxide (0.76 g, 10.87 mmol) was added drop wise at a rapid rate. After 5 minutes, 2-(3-chloro-5-hydroxymethyl-pyridin-2-yl)-2-methyl-propionitrile (0.95 g, 4.53 mmol) from step 1 above, in dry CH_2Cl_2 (5 mL) was added via cannula followed by triethylamine (3.16 g, 22.65 mmol). The reaction was stirred at -50 °C for 30 additional minutes and then allowed to reach room temperature. The reaction was poured into water (150 mL) and extracted with EtOAc (2X 50 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (0-20 % EtOAc in hexanes) to give the product (0.58 g, 62% yield) as a clear oil. ^1H NMR (400MHz, $CDCl_3$): δ 1.90 (s, 6 H), 8.20 (s, 1 H), 8.93 (s, 1 H), 10.12 (s, 1 H). ESMS (MH+): 209.

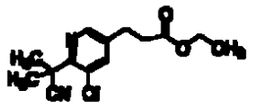
Step 3: 3-[5-Chloro-6-(cyano-dimethyl-methyl)-pyridin-3-yl]-acrylic acid ethyl ester



A solution of 2-(3-chloro-5-formyl-pyridin-2-yl)-2-methyl-propionitrile (0.56 g, 2.76 mmol) from step 3 above and (carbethoxymethylene)triphenylphosphorane (1.26 g, 3.61 mmol) in dry THF (12 mL) was heated to 55 °C and maintained at this temperature overnight.

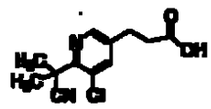
The solvents were removed and the residue was purified by flash column chromatography (0-20 % EtOAc in hexanes) to give the product (0.74 g, 99% yield) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.35 (t, J = 7.7 Hz, 3 H), 1.67 (s, 6 H), 4.29 (q, J = 14, 7.7Hz, 2 H), 6.53 (d, J = 16 Hz, 1 H), 7.55 (d, J = 16 Hz, 1 H), 7.87 (d, J = 2 Hz, 1 H), 8.58 (d, J = 2 Hz, 1 H). ESIMS (MH+): 279.

Step 4: 3-[5-Chloro-6-(cyano-dimethyl-methyl)-pyridin-3-yl]-propionic acid ethyl ester



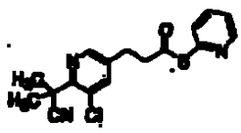
To a solution of 3-[5-chloro-6-(cyano-dimethyl-methyl)-pyridin-3-yl]-acrylic acid ethyl ester (0.74 g, 2.65 mmol) from step 3 above was added ethanol (10 mL) and $Pd(OH)_2/C$ (0.37 g). The reaction was placed under a hydrogen atmosphere using a balloon filled with hydrogen. The slurry was stirred vigorously for 1 hour. The reaction was filtered to remove all of the solids, and the liquid was concentrated to an white solid which was used in next reaction without further purification. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.25 (t, J = 7.7 Hz, 3 H), 1.65 (s, 6 H), 2.62-2.66 (m, 2 H), 2.92-2.96 (m, 2 H), 4.15 (q, J = 14, 7.7Hz, 2 H), 7.51 (d, J = 2 Hz, 1 H), 8.3 (d, J = 2 Hz, 1 H). ESIMS (MH+): 269.

Step 5: 3-[5-Chloro-6-(cyano-dimethyl-methyl)-pyridin-3-yl]-propionic acid



To a stirred solution of 3-[5-chloro-6-(cyano-dimethyl-methyl)-pyridin-3-yl]-propionic acid ethyl ester (0.68g, 2.43 mmol) from step 4 above, in 1:1 THF/H_2O (4mL) was added 2 N NaOH (2.43 mL). The resulting solution was stirred at 60 °C for 1 hour. Solvents were removed and residue was partitioned between ethyl acetate and 10% citric acid and extracted. The organic phase was washed with brine (50 mL), dried over Na_2SO_4 and evaporated. The residue solidified to a white solid and was used without further purification. (0.39 g, 64%) as a white solid. ESIMS (MH-): 251.

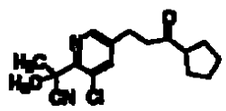
Step 6: 3-Cyclohexyl-thiopropionic acid S-pyridin-2-yl ester



3-[5-Chloro-6-(cyano-dimethyl-methyl)-pyridin-3-yl]-propionic acid (0.39 g, 1.54 mmol) from step 5 above, triphenylphosphine (0.53 g, 2.01 mmol) and 2,2'-dipyridyl disulfide (0.44 g, 2.01 mmol) were combined successively in CH_2Cl_2 (7 mL). The reaction mixture was stirred 4 hours. The solvents were removed and the residue was purified by flash column

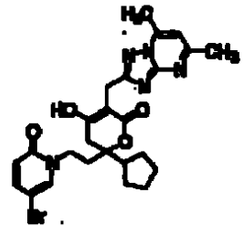
chromatography (0-50% % EtOAc in hexanes) to give the product as a white solid. ESIMS (M+H+): 348

Step 7: 2-[3-Chloro-5-(3-cyclopentyl-3-oxo-propyl)-pyridin-2-yl]-2-methyl-propionitrile



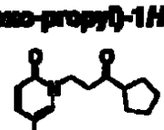
Cyclopentylmagnesium bromide 2.M solution in ether (0.54 mL, 1.10 mmol) was added to a cooled –78 °C solution of 3-cyclohexyl-thiopropionic acid *S*-pyridin-2-yl ester (0.26 g, 1.10mmol), from step 6 above, dissolved in THF (5 mL). The reaction mixture was stirred for 2 min at -78°C and then warmed up to room temperature. The reaction was quenched with 1N HCl and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine, dried over $Na_2SO_4$and concentrated. The residue was purified by silica gel chromatography (0% to 30% EtOAc in hexanes) to give the title compound as a clear oil (0.25g, 78%). ^1H NMR (400MHz, $CDCl_3$): δ 1.62-1.8 (m, 8H), 1.84 (s, 6 H), 2.78-2.92 (m, 4 H), 7.56 (s, 1 H), 8.31 (s, 1 H). ESIMS (M+H+): 305.

Example B(30): 5-Bromo-1-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)pyridin-2(1H)-one



The title compound was prepared analogously to example A(101), where 5-bromo-1-[2-(2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-ethyl]-1*H*-pyridin-2-one was substituted in place of (4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-ethyl-phenyl)-acetonitrile. ^1H NMR (300 MHz, DMSO-d_6): δ 1.33-1.70 (m, 9H), 2.07-2.25 (m, 2 H), 2.53 (s, 3 H), 2.56 (s, 3 H), 2.69 (s, 1 H), 3.68-3.82 (m, 2 H), 3.82-4.00 (m, 2 H), 6.32-6.35 (m, 1 H), 7.01 (s, 1 H), 7.47-7.51 (m, 1 H), 8.01-8.02 (m, 1 H). Anal. Calcd. For $C_{25}H_{28}BrN_5O_4.1.2H_2O$: C, 53.23; H, 5.43; N, 12.42. Found: C, 53.30; H, 5.32; N, 12.03.

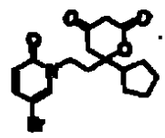
Step 1: 5-Bromo-1-(3-cyclopentyl-3-oxo-propyl)-1*H*-pyridin-2-one



To a solution of 5-Bromo-1*H*-pyridin-2-one (0.53g, 3 mmol) and 1-Cyclopentyl-propenone (0.36 g, 3 mmol) in anhydrous acetonitrile/DMF (10mL/5mL) was added CsF (46

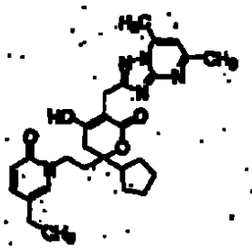
mg, 0.3 mmol). The reaction was stirred at room temperature for 4.5 hours. The solvent was removed in vacuo and the mixture was purified by flash column chromatography (SiO_2, EtOAc in hexanes) to afford the desired product (400mg, 45% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 1.56-1.80 (m, 9H), 2.99-3.02 (m, 2 H), 4.11-4.15 (m, 2 H), 6.44-6.47 (m, 1 H), 7.32-7.35 (m, 1 H), 7.61-7.62 (m, 1H).

Step 2: 5-Bromo-1-[2-(2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-ethyl]-1*H*-pyridin-2-one



Methyl acetoacetate (0.44 mL, 4.04 mmol) dissolved in THF at 0 °C was treated with NaH (60%, 162 mg) and stirred at that temperature for 10 min before it was cooled further down to –40 °C. n-BuLi (2.5 M in hexanes, 1.6 mL) was added slowly and stirring was continued for 10 min before 5-bromo-1-[2-(2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-ethyl]-1*H*-pyridin-2-one (400 mg, 1.35 mmol) was added as a solution in THF. The solution was slowly warmed up to room temperature and stirred for additional 2 hours before it was quenched by the addition of H_2O. The mixture was extracted with EtOAc and the organic phase was washed with brine and dried over $MgSO_4$. The solvent was removed in *vacuo* and the crude was taken up directly into next step. The crude product from previous step was dissolved in THF and treated with 0.1 N NaOH (5 mL) for 15 hours. The reaction was acidified to pH 1 with 1.0 N HCl and the extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated in *vacuo* to afford the desired product (220 mg, 43% for two steps). ^1H NMR (300 MHz, $CDCl_3$): δ 1.39-1.82 (m, 9 H), 2.16-2.24 (m, 2 H), 2.77-2.89 (m, 2 H), 3.41-3.57 (m, 2 H), 3.92-4.15 (m, 2 H), 6.48-6.49 (m, 1 H), 7.35-7.40 (m, 2H).

Example B(31): 1-(2-(2-Cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-5-ethylpyridin-2(1H)-one

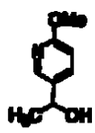


The title compound was prepared analogously to example B(30), where 5-ethyl-1*H*-pyridin-2-one was substituted in place of 5-bromo-1*H*-pyridin-2-one. ^1H NMR (300 MHz,

260
261

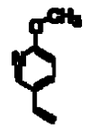
DMSO-d_6): δ 1.36 (t, J = 7.5 Hz, 3H), 1.61-1.97 (m, 9H), 2.31-2.42 (m, 2H), 2.53-2.63 (m, 2H), 2.77 (s, 3 H), 2.79 (s, 3 H), 2.86-3.01 (m, 2 H), 3.93-4.01 (m, 2H), 4.25 (s, 1 H), 6.54-6.57 (m, 1H), 7.29 (s, 1H), 7.55-7.59 (m, 1H), 7.70-7.71 (m, 1 H).

Step 1: 1-(6-Methoxy-pyridin-3-yl)-ethanol



To a solution of 5-bromo-2methoxy-pyridine (19.3 g, 103 mmol) in anhydrous Et_2O (200 mL) at −78 °C was added n-BuLi (2.5 M in hexanes, 50 mL) over 30 min. The resulting mixture was stirred at that temperature for addition 30 min before acetaldehyde (5 mL) was added. The reaction was slowly warmed up to room temperature and the solvent was removed in vacuo. The residue was purified by flash column chromatography to afford the desired product (14.3 g, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (d, J = 6.0 Hz, 3 H), 3.93 (s, 3 H), 4.87-4.92 (m, 1 H), 6.75 (d, J = 8.0 Hz, 3 H), 7.63-7.66 (m, 1 H), 8.12-8.14 (m, 1 H).

Step 2: 2-Methoxy-5-vinyl-pyridine



To a solution of 1-(6-methoxy-pyridin-3-yl)-ethanol (14.3 g, 93.5 mmol) in anhydrous THF was added triethylamine (32.3 mL), followed by MsCl (8.6 mL, 112 mmol). The resulting mixture was stirred at room temperature for 16 hours before it was filtered through a pad of celite. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography to afford the desired product (4.7 g, 37% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94 (s, 3 H), 5.20-5.23 (m, 1H), 5.61-5.67 (m, 1 H), 6.60-6.76 (m, 2 H), 7.67-7.72 (m, 1 H), 8.12 (s, 1 H).

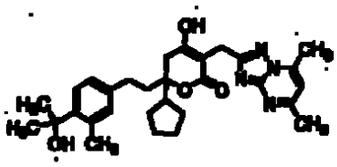
Step 3: 5-Ethyl-1*H*-pyridin-2-one



To a solution of 2-methoxy-5-vinyl-pyridine (2 g) in anhydrous MeOH was added Pd/C (10wt%, 100 mg). The mixture was stirred under H2 atmosphere for 5 hours before it was filtered through a pad of celite. The solvent was removed in vacuo and the residue was taken directly into next step without further purification. The crude product from previous step was dissolved in anhydrous MeCN. To this solution was added NaI (3.3 g, 21.9 mmol) and

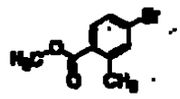
TMSCl (2.8 mL, 21.9 mmol). The resulting mixture was heated to 65 °C for 5 hours before it was filtered through a pad of celite. The filtrate was concentrated in *vacuo* and the residue was purified by flash column chromatography to afford the desired product (1.5 g, 63% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (t, *J* = 7.5 Hz, 3 H), 2.39-2.49 (*m*, 2 H), 6.50-6.58 (*m*, 1 H), 7.15 (s, 1 H), 7.35-7.45 (*m*, 1 H).

Example B(32): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-[4-(1-hydroxy-1-methylethyl)-3-methylphenyl]ethyl]-5,6-dihydro-2H-pyran-2-one



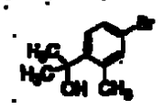
The title compound was prepared analogously to example B(1) where 2-(4-bromo-2-methyl-phenyl)-propan-2-ol was substituted in place of the bromide in step 2 of example B(2). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.51 - 1.60 (m, J=11.31, 5.94, 5.75 Hz, 6 H) 1.61 (s, 6 H) 1.83 - 1.95 (m, 2 H) 1.97 - 2.03 (*m*, J=8.95, 5.31, 5.16 Hz, 2 H) 2.34 - 2.40 (m, 1 H) 2.52 (s, 3 H) 2.55 (d, J=7.83 Hz, 1 H) 2.61 (dd, J=11.62, 5.81 Hz, 3 H) 2.68 (s, 3 H) 2.78 (s, 3 H) 4.08 - 4.12 (m, 2 H) 6.83 (s, 1 H) 6.90 - 6.94 (m, 2 H) 7.31 (d, J=7.83 Hz, 1 H). MS (ESI): 501 $(M+H-H_2O)^+$.

Step 1: 4-Bromo-2-methyl-benzoic acid methyl ester



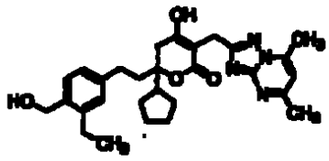
To a solution of 4-bromo-2-methyl-benzoic acid 10.0 g, 46.5 mmol) in methanol (100 mL) at room temperature was added sulfuric acid (conc. 1 mL) dropwise. The solution was heated at reflux for 18 h. The solution was removed from heat and sulfuric acid (conc. 0.5 mL) was added. The solution was heated at reflux 2h then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with saturated sodium bicarbonate, then with saturated sodium chloride. The solution was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a crude colorless oil. Flash chromatography (SiO_2, 5% ethyl acetate/hexane) gave the title compound as a colorless oil (9.2 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.58 (s, 3 H) 3.89 (s, 3 H) 7.38 (dd, J=8.46, 1.89 Hz, 1 H) 7.42 (d, J=1.82 Hz, 1 H) 7.76 (d, J=8.34 Hz, 1 H).

Step 2: 2-(4-Bromo-2-methyl-phenyl)-propan-2-ol



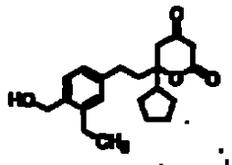
To 4-bromo-2-methyl-benzoic acid methyl ester (3.7 g, 15.9 mmol) in diethyl ether (10 mL) at 0°C under N_2 was added 3N methylmagnesium bromide in diethyl ether (21 mL, 63 mmol). The mixture was stirred 18 h at room temperature. The mixture was poured into 1N hydrochloric acid (aq, 10 mL) and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a crude colorless oil. Flash chromatography (SiO_2, 5% ethyl acetate/hexane) gave the title compound as a colorless oil (2.6 g, 72%). ^1H NMR (300 MHz, $CDCl_3$): δ ppm 1.63 (s, 6 H) 2.56 (s, 3 H) 7.26 - 7.34 (m, 3 H).

Example B(33): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-[3-ethyl-4-(hydroxymethyl)phenyl]ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



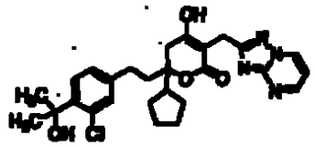
The title compound was prepared analogously to example B(1) where 6-cyclopentyl-6-[2-[3-ethyl-4-(hydroxymethyl)phenyl]ethyl]dihydro-2H-pyran-2,4(3H)-dione (Example B(34)) was substituted in place of 6-[2-(3-chloro-4-methanesulfonyl-phenyl)-ethyl]-6-cyclopentyl-dihydro-pyran-2,4-dione in that example. Yield (60 mg, 23%). ^1H NMR (300 MHz, $CDCl_3$): δ ppm 1.24 (t, *J*=7.25 Hz, 3 H) 1.53 - 1.84 (m, 8 H) 1.96 - 2.02 (m, 2 H) 2.32 - 2.42 (m, 1 H) 2.49 - 2.58 (m, 2 H) 2.65 (s, 3 H) 2.67 - 2.73 (m, 6 H) 2.76 (s, 3 H) 4.06 (s, 1 H) 4.66 (s, 2 H) 6.83 (s, 1 H) 6.94 - 7.01 (m, 2 H) 7.22 (d, *J*=7.54 Hz, 1 H). MS (ESI): 506 $(M+H)^+$.

Example B(34): 6-Cyclopentyl-6-[2-[3-ethyl-4-(hydroxymethyl)phenyl]ethyl]dihydro-2H-pyran-2,4(3H)-dione



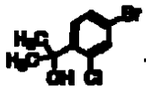
The title compound was prepared analogously to example B(2) where (4-bromo-2-ethyl-phenyl)-methanol was substituted in place of the bromide in that example. ^1H NMR (300 MHz, $CDCl_3$): δ ppm 1.22 (t, *J*=7.54 Hz, 3 H) 1.60 - 1.75 (m, 8 H) 1.91 - 2.04 (m, 3 H) 2.22 - 2.33 (m, 1 H) 2.61 - 2.73 (m, 4 H) 2.76 (s, 2 H) 3.41 (s, 2 H) 4.66 (s, 2 H) 6.96 - 7.00 (m, 2 H) 7.28 (d, *J*=8.29 Hz, 1 H). MS (ESI): 367 $(M+Na)^+$.

Example B(35): 6-[2-[3-Chloro-4-(1-hydroxy-1-methylethyl)phenyl]ethyl]-6-cyclopentyl-4-hydroxy-3-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-5,6-dihydro-2H-pyran-2-one



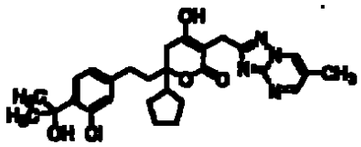
The title compound was prepared analogously to example B(1) where 2-(4-bromo-2-chloro-phenyl)-propan-2-ol was substituted in place of the bromide in step 2 of example B(2) that example and methoxy-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl-methanol was substituted in place of 5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde in Example A(1). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.58 (d, J=9.04 Hz, 6 H) 1.68 (s, 6 H) 1.94 - 2.05 (m, 2 H) 2.33 - 2.44 (m, 1 H) 2.46 - 2.55 (m, 1 H) 2.60 - 2.68 (m, 2 H) 2.70 - 2.80 (m, 1 H) 4.11 (d, J=2.45 Hz, 2 H) 7.01 (dd, J=8.19, 1.79 Hz, 1 H) 7.12 (d, J=1.70 Hz, 1 H) 7.14 - 7.21 (m, 1 H) 7.51 (d, J=8.10 Hz, 1 H) 8.51 - 8.55 (m, 2 H). MS (ESI): 533 $(M+Na)^+$.

Step 1: 2-(4-Bromo-2-chloro-phenyl)-propan-2-ol



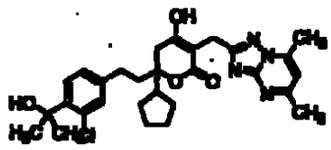
The title compound was prepared analogously to example B(32) (Step 2) where 4-bromo-2-chloro-benzoic acid was substituted in place of 4-bromo-2-methyl-benzoic acid. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.71 (s, 6 H), 7.36-7.40 (m, 1 H), 7.52 (m, 1 H), 7.57-7.60 (m, 1 H).

Example B(36): 6-[2-[3-Chloro-4-(1-hydroxy-1-methylethyl)phenyl]ethyl]-6-cyclopentyl-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one



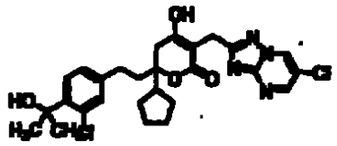
The title compound was prepared analogously to B(35) where 6-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde was substituted in place of methoxy-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl-methanol in that example. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.57 (m, 6 H) 1.62 (s, 3 H) 1.68 (s, 6 H) 1.70 (d, J=6.26 Hz, 3 H) 1.94 - 2.08 (m, 2 H) 2.34 - 2.43 (m, 1 H) 2.47 (s, 3 H) 2.59 - 2.67 (m, 2 H) 2.74 (d, J=17.94 Hz, 1 H) 4.08 (d, J=2.76 Hz, 1 H) 7.01 (dd, J=7.95, 1.84 Hz, 1 H) 7.12 (d, J=1.77 Hz, 1 H) 7.50 (d, J=8.08 Hz, 1 H) 8.60 (d, J=1.26 Hz, 1 H) 8.68 (d, J=2.27 Hz, 1 H). MS (ESI): 547 $(M+Na)^+$.

Example B(37): 6-[2-[3-Chloro-4-(1-hydroxy-1-methylethyl)phenyl]ethyl]-6-cyclopentyl-3-[(6,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



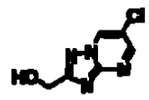
The title compound was prepared analogously to example B(1) where 2-(4-bromo-2-chloro-phenyl)-propan-2-ol was substituted in place of the bromide in step 2 of example B(2). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.55 (s, 1 H) 1.64 - 1.71 (m, 12 H) 1.94 - 2.03 (m, 2 H) 2.30 - 2.43 (m, 2 H) 2.50 (d, J=17.90 Hz, 2 H) 2.58 - 2.64 (m, 2 H) 2.64 - 2.72 (m, 5 H) 2.78 (s, 3 H) 4.07 (s, 2 H) 6.83 (s, 1 H) 6.99 - 7.04 (m, 1 H) 7.11 (d, J=1.13 Hz, 1 H) 7.50 (d, J=8.10 Hz, 1 H). MS (ESI): 551 $(M+Na)^+$. Anal. Calcd. For $C_{29}H_{33}ClN_4O_4$: 1.5 AcOH C, 61.09; H, 6.57; N, 8.91. Found: C, 61.22; H, 6.50; N, 8.85.

Example B(35): 6-[2-[3-Chloro-4-(1-hydroxy-1-methylethyl)phenyl]ethyl]-3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-4-hydroxy-5,6-dihydro-2H-pyran-2-one



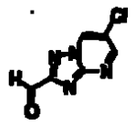
The title compound was prepared analogously to B(35) where 6-chloro-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde from step 2 below was substituted in place of methoxy-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl-methanol in that example. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.34 (s, 1 H) 1.48 - 1.59 (m, 10 H) 1.63 - 1.70 (m, 2 H) 2.08 (d, J=19.95 Hz, 2 H) 2.34 - 2.44 (m, J=6.84 Hz, 1 H) 2.52 - 2.61 (m, J=16.42 Hz, 3 H) 2.76 (d, J=17.43 Hz, 1 H) 3.29 - 3.41 (m, 3 H) 3.73 - 3.85 (m, 1 H) 5.19 (s, 1 H) 7.16 (dd, J=8.92, 2.40 Hz, 2 H) 7.70 (d, J=8.59 Hz, 1 H) 8.85 (d, J=2.53 Hz, 1 H) 9.57 (d, J=2.53 Hz, 1 H). Anal. Calcd. For $C_{27}H_{30}Cl_2N_4O_4$: H_2O C, 57.55; H, 5.72; N, 9.94. Found: C, 57.57; H, 5.81; N, 9.72.

Step 1: (6-Chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methanol



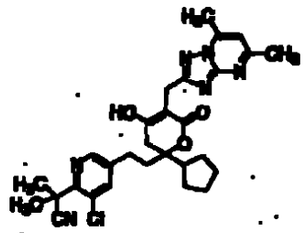
To a slurry of (5-amino-1H-[1,2,4]triazol-3-yl)-methanol (29.5 g, 160 mmol, from step 6 of example A(1)) in acetic acid was added chloromalonaldehyde (16 g, 150 mmol). The mixture was heated to 80 °C for 4 hours. Upon cooling of the reaction, the product crystallized out as a white solid (25.5 g, 92%). ^{1}H NMR (300MHz, DMSO-d_6): δ 4.67 (s, 2 H), 5.62 (s, 1 H), 8.94 (d, J=2.45 Hz, 1 H), 9.81 (d, J=2.45 Hz, 1 H).

Step 2: 6-Chloro[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde



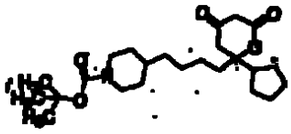
A mixture of (6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methanol (9.86 g, 53.4 mmol), TEMPO (828 mg, 7.2 mmol), Iodobenzene diacetate (18.9 g, 59 mmol) in CH_2Cl_2 (75 mL) was stirred at room temperature for 2 hours. Once the reaction was deemed complete, methyl-tert-butyl ether (50 mL) was added slowly to precipitate the product as a white solid (8.72 g, 90%). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.93 (d, J=2.45 Hz, 1 H), 8.99 (d, J=2.64 Hz, 1 H), 10.25 (s, 1 H). MS (APCI): 183.0, 185.0 ($M+H^+$).

Example B(39): 2-[3-Chloro-5-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)pyridin-2-yl]-2-methylpropanenitrile



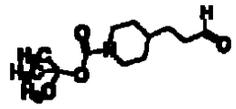
The title compound was prepared analogously to example A(1) where 2-[3-chloro-5-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)ethyl]pyridin-2-yl]-2-methylpropanenitrile (Example B(29)was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione of that example. ^1H NMR (400MHz, DMSO-d_6): δ 1.22-1.54 (m, 10 H), 1.59 (s, 6 H), 1.90-2.02 (m, 1 H), 2.30-2.35 (m, 8 H), 2.37-2.59 (m, 2 H), 3.54 (d, J = 16 Hz, 1 H), 3.64 (d, J = 16 Hz, 1 H), 6.55 (s, 1 H), 7.74 (s, 1 H), 8.27 (s, 1 H), 11 (s, 1 H). . ESMS (M+H+): 549.

Example B(40): tert-Butyl 4-[4-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)butyl]piperidine-1-carboxylate



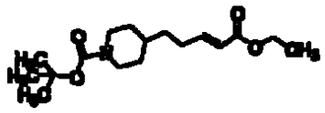
The title compound was prepared analogously to example B(2)where 4-(5-cyclopentyl-5-oxo-pentyl)-piperidine-1-carboxylic acid tert-butyl ester from step 6 belowwas substituted in place of 3-(3-chloro-4-methanesulfonyl-phenyl)-1-cyclopentyl-propan-1-one of that example. ^1H NMR (400MHz, $CDCl_3$): δ 1.06-1.69 (m, 29H), 2.05-2.22 (m, 2H), 2.58-2.78 (m, 4H), 3.40 (s, 2H), 4.0-4.11 (m, 2H). ESMS (M+H+): 422.

Step 1: 4-(3-Oxo-propyl)-piperidine-1-carboxylic acid *tert*-butyl ester



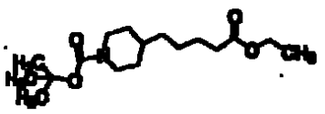
The title compound was prepared analogously to step 2 of example B(29) where 4-(3-hydroxy-propyl)-piperidine-1-carboxylic acid *tert*-butyl was substituted in place of 2-(3-chloro-5-hydroxymethyl-pyridin-2-yl)-2-methyl-propionitrile in that example. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.07-1.17 (m, 2H), 1.34-1.43 (m, 1H), 1.45 (s, 9H), 1.55-1.67 (m, 4H), 2.45-2.50 (m, 2H), 2.62-2.71 (m, 2H), 4.09-4.14 (m, 2H), 9.78 (s, 1H). ESIMS (MH+): 242.

Step 2: 4-(4-Ethoxycarbonyl-but-3-enyl)-piperidine-1-carboxylic acid *tert*-butyl ester



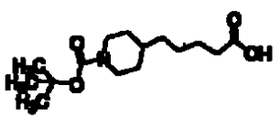
The title compound was prepared analogously to step 3 of example B(29)where 4-(3-oxo-propyl)-piperidine-1-carboxylic acid *tert*-butyl ester from step 1 above, was substituted in place of 2-(3-chloro-5-formyl-pyridin-2-yl)-2-methyl-propionitrile of that example. ^{1}H NMR (400MHz, $CDCl_3$): δ 0.95-1.08 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3 H), 1.32-1.35 (m, 3H), 1.38 (s, 9H), 1.56-1.60 (m, 2H), 2.09-2.19 (m, 2H), 2.5-2.63 (m, 2H), 3.97-3.99 (m, 2H), 4.11 (q, *J* = 7.2 Hz, 2 H), 5.74 (dd, *J* = 15.6, 1.5 Hz, 1 H), 6.82-6.93 (m, 1H). ESIMS (MH+): 312.

Step 3: 4-(4-Ethoxycarbonyl-butyl)-piperidine-1-carboxylic acid *tert*-butyl ester



The title compound was prepared analogously to step 4 of example B(29)where 4-(4-ethoxycarbonyl-but-3-enyl)-piperidine-1-carboxylic acid *tert*-butyl ester from step 2 above, was substituted in place of 3-[5-chloro-6-(cyano-dimethyl-methyl)-pyridin-3-yl]-acrylic acid ethyl ester of that example. ^{1}H NMR (400MHz, $CDCl_3$): δ 0.99-1.12 (m, 2H), 1.23-1.40 (m, 5H), 1.45 (s, 9H), 1.56-1.66 (m, 4H), 2.27-2.32 (m, 2H), 2.61-2.70 (m, 2H), 4.04-4.16 (m, 4H). ESIMS (MH+): 314.

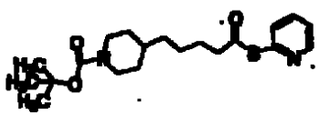
Step 4: 4-(4-Carboxy-butyl)-piperidine-1-carboxylic acid *tert*-butyl ester



The title compound was prepared analogously to step 5 of example B(29)where 4-(4-ethoxycarbonyl-butyl)-piperidine-1-carboxylic acid *tert*-butyl ester from step 3 above, was substituted in place of 3-[5-chloro-6-(cyano-dimethyl-methyl)-pyridin-3-yl]-propionic acid ethyl

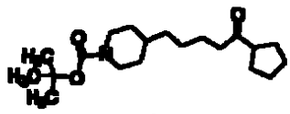
ester in that example. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.07-1.39 (m, 7H), 1.45 (s, 9H), 1.59-1.70 (m, 4H), 2.33-2.38 (m, 2H), 2.64-2.68 (m, 2H), 4.09-4.12 (m, 2H). ESIMS (MH-): 284.

Step 5: 4-[4-(Pyridin-2-ylsulfanylcarbonyl)-butyl]-piperidine-1-carboxylic acid tert-butyl ester



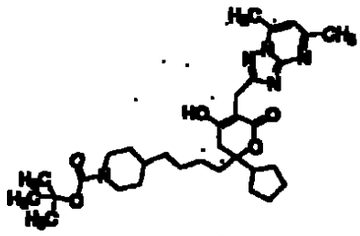
The title compound was prepared analogously to step 6 of example B(29)where 4-(4-carboxy-butyl)-piperidine-1-carboxylic acid tert-butyl ester from step 4 above, was substituted in place of 3-[5-chloro-6-(cyano-dimethyl-methyl)-pyridin-3-yl]-propionic acid of that example. ESIMS (MH+): 379.

Step 6: 4-(5-Cyclopentyl-5-oxo-pentyl)-piperidine-1-carboxylic acid tert-butyl ester



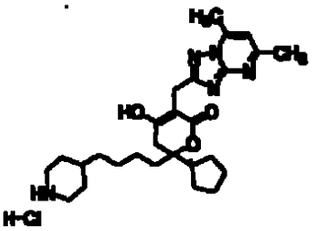
The title compound was prepared analogously to step 7 of example B(29)where 4-[4-(pyridin-2-ylsulfanylcarbonyl)-butyl]-piperidine-1-carboxylic acid tert-butyl ester from step 5 above, was substituted in place 3-cyclohexyl-thiopropionic acid S-pyridin-2-yl ester. ^{1}H NMR (400MHz, $CDCl_3$): δ 1-1.42 (m, 8H), 1.45 (s, 9H), 1.50-1.84 (m, 14H), 2.42-2.46 (m, 2H), 2.62-2.7 (m, 2H), 2.82-2.87 (m, 1H). ESIMS (MH+): 337.

Example B(41): tert-Butyl 4-(4-(2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)butyl)piperidine-1-carboxylate



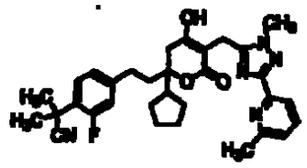
The title compound was prepared analogously to example A(1) where tert-butyl 4-[4-(2-cyclopentyl-4,6-dioxotetrahydro-2H-pyran-2-yl)butyl]piperidine-1-carboxylate (example B(40)) was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione of that example. ^{1}H NMR (400MHz, DMSO-d_6): δ 0.76-1.60 (m, 29 H), 1.90-1.94 (m, 4 H), 2.27-2.6 (m, 8 H), 3.54-3.74 (m, 4H), 6.92 (s, 1H), 10.62 (s, 1H). ESIMS (MH+): 582.

Example B(42): 6-Cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5-(4-piperidin-4-ylbutyl)-5,6-dihydro-2H-pyran-2-one



tert-Butyl 4-(4-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]butyl)piperidine-1-carboxylate (example B(41)) (0.47 g, 0.8 mmol) was dissolved in dioxane (1 mL) and 4N HCl in dioxane (1 mL). The reaction was stirred overnight at room temperature. Solvents were removed and the residue was purified using a Dionex system (30-70% CH3CN/H2O (0.1% AcOH). H NMR (400MHz, DMSO-d_6): δ 1.37-1.70 (m, 20 H), 2.65-2.85 (m, 12 H), 3.59-3.95 (m, 4H), 7.95 (s, 1H), 11.12 (s, 1H). Anal. Calcd. For $C_{30}H_{48}N_6O_3$·1.0 HCl·1.5 H_2O: C, 59.49; H, 7.95; N, 12.85, Found: C, 59.60; H, 8.04; N, 12.95. ESIMS (M+H+): 482.

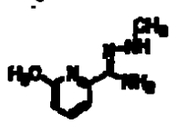
Example B(43): 2-{4-[2-(2-Cyclopentyl-4-hydroxy-5-[[1-methyl-3-(6-methylpyridin-2-yl)-1H-1,2,4-triazol-5-yl]methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl]-2-fluorophenyl}-2-methylpropanenitrile



A solution of 2-{4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-2-methyl-propionitrile (1.0 g, 2.70 mmol, from step 3 of example A(84) in hot (50 °C) isopropanol (7 mL) was treated with $(CH_3)_2NHBH_3$ (175 mg, 2.97 mmol, 1.1 equiv), then with a solution of 1-methyl-3-(6-methylpyridin-2-yl)-1*H*-1,2,4-triazole-5-carbaldehyde hydrochloride hydrate (762 mg, 2.97 mmol, 1.1 equiv, from Step 4 below) in isopropanol (4 mL) containing triethylamine (301 mg, 2.97 mmol, 1.1 equiv). The reaction mixture was stirred heated at 47-50 °C for 18 h. The reaction mixture was treated with 1.1 equiv of 1 M aqueous HCl and concentrated *in vacuo* to afford an oily resin. This was diluted with water and extracted with dichloromethane containing 10% methanol (3 x 30 mL). The extract was dried over Na_2SO_4, filtered, and concentrated. The residue was triturated with hot ethyl acetate/methylene chloride, filtered, washed with cold ether, and dried, affording 884 mg (39%) of the title product. ^{1}H NMR (400MHz, DMSO-d_6): δ 1.36-1.71 (m, 14 H), 2.05 (m, 2 H), 2.48 (m, 1 H), 2.48 (s, 3 H), 2.68 (m, 3 H), 2.76 (d, J=17.9 Hz, 1 H), 3.67(d, J=15.7 Hz, 1 H), 3.74(d, J=15.7 Hz, 1 H), 3.91 (s, 3

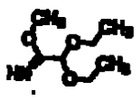
H), 6.99(d, J=8.1 Hz, 1 H), 7.10-7.20 (m, 3 H), 7.57 (m, 2 H), 11.22 (s, 1 H). LC-MS (APCI) calcd for $C_{28}H_{28}FN_5O_3$: 557.28, found ($M+H^+$): 558.40 m/z.

Step 1: *N',6*-Dimethylpyridine-2-carbohydrazonamide



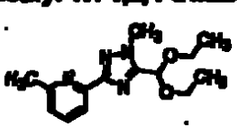
6-Methylpyridine-2-carbonitrile (45.3 g, 0.384 mol) and methylhydrazine (94 mL, 5.30 mol) were mixed with ethanol (200 mL). The mixture was stirred at room temperature overnight, and then an additional portion (18 mL, 1.00 mol) of methylhydrazine was added, and the mixture was stirred for a further 16 h. The mixture was then evaporated to give 58.0 g of crude *N',6*-dimethylpyridine-2-carbohydrazonamide (~82% yield), which was used for the next stage of the synthesis without additional purification.

Step 2: Methyl 2,2-diethoxyethanimidoate



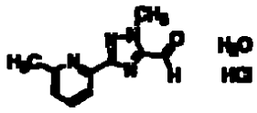
A solution of diethoxyacetonitrile (75 g, 0.579 mol) in methanol (210 mL) was added at room temperature to a solution of sodium methoxide (28.3 g, 0.522 mol) in methanol (450 mL). The mixture was stirred overnight, and then the methanol was carefully evaporated (volatile product). The residue was diluted with dichloromethane (200 mL) and water (300 mL). The organic layer was separated, and the aqueous one was extracted with dichloromethane (2 x 150 mL). The combined organic layer was dried over Na_2SO_4 and evaporated to give 83 g of crude methyl 2,2-diethoxyethanimidoate (~80% yield).

Step 3: 2-[5-(Diethoxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl]-6-methylpyridine



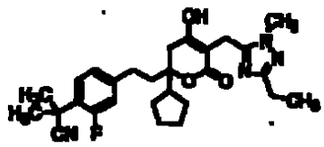
Methyl 2,2-diethoxyethanimidoate (42 g, 0.26 mol) was dissolved in methanol (200 mL), and a solution of compound *N',6*-dimethylpyridine-2-carbohydrazonamide (45 g, 0.25 mol) in methanol (200 mL) while cooling with a water bath, followed by the addition of acetic acid (22 mL, 0.37 mol). The mixture was stirred at room temperature for 3 h, and then K_2CO_3 (10 g, 0.071 mol) was added. The mixture was stirred for 10 min, and then the methanol was evaporated. The residue was stirred with a solution of K_2CO_3 (20 g) in water (200 mL), and extracted with ether (2 x 150 mL). The organic layer was washed with water and then saturated NaCl solution, dried over Na_2SO_4 and evaporated. The residue (82 g) was purified by chromatography on a silica gel column to afford 39.5 g (57%) of the title product.

Step 4: : 1-Methyl-3-(6-methylpyridin-2-yl)-1*H*-1,2,4-triazole-5-carbaldehyde hydrochloride hydrate



A mixture of 2-[5-(diethoxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl]-6-methylpyridine (38 g, 0.1377 mol), water (92 mL) and concentrated HCl (23 mL, 0.276 mol) was heated at 70-80 °C for 2 h. The resulting solution was co-evaporated with water four times using a water aspirator vacuum, then dried *in vacuo* at 60 °C to give 33.5 g (94.5%) of the title product as a covalently-bound hydrate. Satisfactory *C,H,N*-analysis was obtained. ^{1}H NMR (400MHz, D_2O+TFA): δ 2.90 (s, 3H), 4.13 (s, 3H), 6.36 (s, 1H), 7.94 (d, *J* = 8 Hz, 1H), 8.37 (d, *J* = 8 Hz, 1H), 8.56 (t, *J* = 8 Hz, 1H). LC-MS (API-ES) calcd for $C_{10}H_{10}N_4O$: 202.09, found (M+H$^+$): 203.1; (M+18+H$^+$) 221.1 m/z.

Example B(44): 2-[4-(2-[2-cyclopentyl-5-[(3-ethyl-1-methyl-1H-1,2,4-triazol-5-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile



The title compound was prepared analogously to example B(43) where 3-ethyl-1-methyl-1*H*-1,2,4-triazole-5-carbaldehyde hydrochloride hydrate (step 4, below) was substituted in place of 1-methyl-3-(6-methylpyridin-2-yl)-1*H*-1,2,4-triazole-5-carbaldehyde. The product was isolated by trituration with ether. Yield 552 mg, 41%. ^{1}H NMR (400MHz, DMSO-d_6): δ 1.03 (d, *J*=7.6 Hz, 3 H), 1.34-1.76 (m, 14 H), 2.08 (m, 2 H), 2.38 (m, 3 H), 2.60 (m, 3 H), 2.78 (d, *J*=17.8 Hz, 1 H), 3.53 (d, *J*=15.9 Hz, 1 H), 3.61 (d, *J*=15.9 Hz, 1 H), 3.73 (s, 3 H), 7.07 (d, *J*=8.6 Hz, 1 H), 7.13 (d, *J*=13.1 Hz, 1 H), 7.35 (t, *J*=8.6 Hz, 1 H). LC-MS (APCI) calcd for $C_{28}H_{35}FN_4O_3$: 494.27, found (M+H$^+$): 495.40 m/z.

Step 1: Methyl propanimidoate hydrochloride



Propionitrile (175 mL, 2.5 mol) was added at 0 °C to 4 M HCl in dioxane (650 mL). Absolute methanol (112 mL) was added dropwise at 0 °C, and the mixture was left to stand at this temperature for 1 h, and then in a refrigerator overnight. The resulting crystalline slurry was treated with ether (700 mL). The crystalline precipitate was separated by filtration, washed with ether to removed residual HCl and dried to give the title product. Yield: 228 g (73%).

Step 2: *N*'-methylpropanehydrazonamide hydrochloride



To a suspension of methyl propanimidoate hydrochloride (100 g, 0.803 mol) in methanol (400 mL) was added a solution of methylhydrazine (47 mL, 0.883 mol) dropwise at room temperature. The solution was allowed to stand at room temperature for 2 days, then evaporated. The resulting oil was washed with THF (3 x 150 mL) and dried to give 84.1 g (81%) of the crude title product.

Step 3: 5-(Diethoxymethyl)-3-ethyl-1-methyl-1*H*-1,2,4-triazole



A solution of sodium methoxide (3.30 g, 0.0611 mol) in methanol (100 mL) was added at room temperature to a solution of diethoxyacetonitrile (78.9 g, 0.611 mol) in methanol (600 mL). The resulting mixture was stirred at room temperature overnight, and a solution of crude *N*'-methylpropanehydrazonamide hydrochloride from Step 2 (84.1 g, ~0.60 mol) in methanol (200 mL) was added. Anhydrous sodium acetate (50.0 g, 0.61 mol) was added, and the resulting mixture was refluxed under an atmosphere of Ar for 20 h. Then methanol was evaporated, and the dark oily residue was extracted with ether (3 x 250 mL). The ether solution was passed through a layer of silica gel, and the filtrate was evaporated. The residue was distilled *in vacuo* to give 35.0 g (27%) of the title product (bp 68 °C at 0.1 mm Hg). Note: There is a higher-boiling second fraction (15 g; bp 120 °C at 0.1 mm Hg) that is a triazole impurity containing two acetal groups.

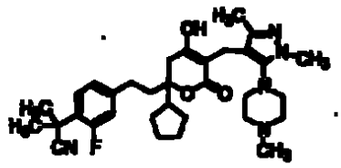
Step 4: 3-Ethyl-1-methyl-1*H*-1,2,4-triazole-5-carbaldehyde hydrochloride hydrate



A solution of 5-(diethoxymethyl)-3-ethyl-1-methyl-1*H*-1,2,4-triazole from Step 3 (35.6 g, 0.167 mol) in 3.6 M HCl (150 mL) was heated (60 °C) for 10 h, then evaporated to dryness. The residual oil was washed with THF (3 x 100 mL), then treated with dry acetone (200 mL) causing crystallization. The product was filtered and dried, affording 18.8 g (59%) of the title product. Satisfactory C,H,N-analysis was obtained. The compound was observed by ^{1}H NMR to be a 60:40 mixture of non-covalent (free aldehyde) and covalent hydrates, respectively: ^{1}H NMR (400MHz, DMSO-d_6): δ 1.22 (m, overlap, 3H), 2.67 (q, J = 7.6 Hz, 0.6 x 2H), 2.79 (q, J = 7.6 Hz, 0.4 x 2H), 3.98 (s, 0.4 x 3H), 4.04 (s, 0.6 x 3H), 6.21 (s, 0.4 x 1H), 8.35 (br s, 3H), 9.87 (s, 0.6 x 1H). LC-MS (APCI) calcd for $C_6H_9N_3O$: 139.07, found (M+H$^+$): 140.1; (M+18+H$^+$) 158.1 m/z.

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Example B(45): 2-(4-[2-(2-cyclopentyl-5-[1,3-dimethyl-5-(4-methylpiperazin-1-yl)-1H-pyrazol-4-yl]methyl}-4-hydroxy-6-oxo-5,6-dihydro-2H-pyran-2-yl)ethyl]-2-fluorophenyl}-2-methylpropanenitrile



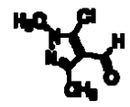
The title compound was prepared analogously to example B(43) where 1,3-dimethyl-5-(4-methylpiperazin-1-yl)-1*H*-pyrazole-4-carbaldehyde (step 3, below) was substituted in place of 1-methyl-3-(6-methylpyridin-2-yl)-1*H*-1,2,4-triazole-5-carbaldehyde, and the triethylamine was omitted. The product was isolated by trituration with ether. Yield 1.0 g (64%). ^{1}H NMR (400MHz, DMSO-d_6): δ 1.31-1.70 (m, 14 H), 1.90 (m, 2 H), 1.95 (s, 3 H), 2.25 (s, 3 H), 2.32 (m, 1 H), 2.43 (m, 4 H), 2.57 (m, 3 H), 2.67 (d, *J*=17.4 Hz, 1 H), 3.06 (m, 4 H), 3.25 (d, *J*=14.8 Hz, 1 H), 3.32 (d, *J*=14.8 Hz, 1 H), 3.48 (s, 3 H), 6.89 (d, *J*=8.1 Hz, 1 H), 7.08 (d, *J*=13.1 Hz, 1 H), 7.35 (t, *J*=8.3 Hz, 1 H). LC-MS (APCI) calcd for $C_{33}H_{44}FN_5O_3$: 577.34, found ($M+H^+$): 578.40 m/z.

Step 1: 1,3-Dimethyl-1*H*-pyrazol-5-ol



To a solution of ethyl acetoacetate (50 g, 0.3846 mol) in methanol (250 mL) was added a solution of methylhydrazine (17.5 g, 0.38 mol) in methanol (20 mL) dropwise over 20 min, resulting in an increase in temperature to 45 °C. The reaction mixture was stirred overnight at room temperature. Methanol was removed under vacuum on a rotary evaporator to give 50 g of the crude title pyrazolone that was used in the next step without purification.

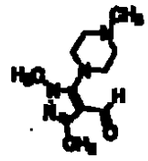
Step 2: 5-Chloro-1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde



To DMF (33.29 mL, 0.458 mol) was carefully added $POCl_3$ (134.16 g, 81.5 mL, 0.874 mol.) at 0 °C. The reaction mixture was diluted with 1,2-dichloroethane (100 mL), then treated with a solution of crude 1,3-dimethyl-1*H*-pyrazol-5-ol (50 g, from Step 1) in dichloroethane (100 mL) under continued stirring at 0 °C. The mixture was refluxed for 3 h, then left to stir overnight at room temperature. In order to decompose the formylating reagent, to the reaction mixture was added a solution of sodium hydroxide (91.2 g, 2.28 mol) in water (200 mL) dropwise at 0 °C. The reaction mixture was diluted with water and extracted with dichloromethane (3 x 250

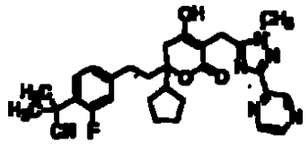
mL). The organic extracts were washed with water to neutral pH, washed with water, then dried with sodium sulfate. The solvent was removed under vacuum to afford the title product (31.1 g, 51% overall from methylhydrazine) as a yellow crystalline substance.

Step 3: 1,3-dimethyl-5-(4-methylpiperazin-1-yl)-1*H*-pyrazole-4-carbaldehyde



To a solution of 5-chloro-1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde (25.4 g, 0.16 mol) in HMPA (25 mL) and water (25 mL) was added 1-methylpiperazine (40 g, 0.4 mol, 2.5 equiv), and the mixture was heated at 120-125 °C for 25 h. When the reaction was completed, the reaction mixture was poured into water (500 mL), and potassium carbonate was added to make the medium strongly alkaline. The mixture was extracted with dichloromethane (5 x 100 mL). The combined organic extracts were washed twice with water and dried with sodium sulfate, and the solvent evaporated. The residue was purified chromatographically on silica gel with gradient elution from dichloromethane to methanol, affording 10.2 g (29%) of the title product. Satisfactory *C,H,N*-analysis was obtained. ^{1}H NMR (400MHz, DMSO-d_6): δ 2.23 (s, 3H), 2.26 (s, 3H), 2.44 (m, 4H), 3.16 (m, 4H), 3.89 (s, 3H), 9.88 (s, 1H). LC-MS (API-ES) calcd for $C_{11}H_{18}N_4O$: 222.15, found ($M+H^+$): 223.1 m/z.

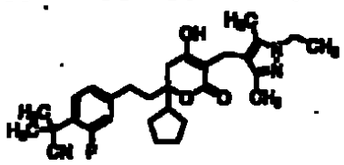
Example B(49): 2-[4-[2-[2-Cyclopentyl-4-hydroxy-5-[(1-methyl-3-pyrazin-2-yl-1H-1,2,4-triazol-5-yl)methyl]-6-oxo-5,6-dihydro-2H-pyran-2-yl]ethyl]-2-fluorophenyl]-2-methylpropanenitrile



The title compound was prepared analogously to example B(15) where 2-[4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl]-2-methyl-propionitrile (from step 3 of example A(84)) was substituted in place of 6-[2-(5-chloro-2,4-dimethoxy-phenyl)-ethyl]-6-cyclopentyl-dihydro-pyran-2,4-dione. The product was chromatographed on silica gel and triturated with ether. Yield = 201 mg (13%). ^{1}H NMR (400MHz, DMSO-d_6): δ 1.35-1.71 (m, 14 H), 2.02 (m, 2 H), 2.39 (s, 1 H), 2.69 (m, 3 H), 2.75 (d, J=17.4 Hz, 1 H), 3.69 (d, J=17.1 Hz, 1 H), 3.76 (d, J=17.1 Hz, 1 H), 3.94 (s, 3 H), 6.99 (d, J=8.1 Hz, 1 H), 7.09 (d, J=13.1 Hz, 1 H), 7.20 (t, J=8.3 Hz, 1 H), 8.60 (s, 1 H), 8.64 (s, 1 H), 8.97 (s, 1 H). LC-MS (APCI) calcd for $C_{29}H_{32}FN_7O_3$: 544.63, found ($M+H^+$): 545.30 m/z.

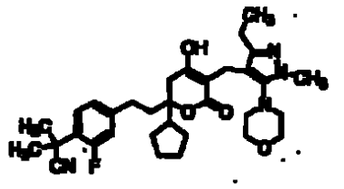
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Example B(47): 2-[4-(2-[2-Cyclopentyl-5-[(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile



The title compound was prepared analogously to example B(43) where 1-ethyl-3,5-dimethyl-1*H*-pyrazole-4-carbaldehyde was substituted in place of 1-methyl-3-(6-methylpyridin-2-yl)-1*H*-1,2,4-triazole-5-carbaldehyde, and the triethylamine was omitted. The product was purified by chromatography on silica gel and trituration with ether. Yield: 795 mg, 58%. ^{1}H NMR (400MHz, DMSO-d_6): δ 1.14 (t, *J*=7.1 Hz, 3 H), 1.29-1.62 (m, 6 H), 1.70 (s, 6 H), 1.82 (m, 2 H), 2.04 (s, 3 H), 2.11 (s, 3 H), 2.28 (m, 1 H), 2.49-2.55 (m, 3 H), 2.69 (d, *J*=17.6 Hz, 1 H), 3.11 (d, *J*=14.6 Hz, 1 H), 3.22 (d, *J*=14.6 Hz, 1 H), 3.94 (q, *J*=7.3 Hz, 2 H), 6.93 (d, *J*=9.6 Hz, 1 H), 7.04 (d, *J*=11.6 Hz, 1 H), 7.34 (t, *J*=8.6 Hz, 1 H), 10.65 (s, 1 H). LC-MS (APCI) calcd for $C_{32}H_{42}FN_3O_3$: 507.29, found (M+H$^+$): 508.40 m/z.

Example B(48): 2-[4-(2-[2-Cyclopentyl-5-[(3-ethyl-1-methyl-5-morpholin-4-yl-1H-pyrazol-4-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile



The title compound was prepared analogously to example B(43) where 3-ethyl-1-methyl-5-morpholin-4-yl-1*H*-pyrazole-4-carbaldehyde (Step 3, below) was substituted in place of 1-methyl-3-(6-methylpyridin-2-yl)-1*H*-1,2,4-triazole-5-carbaldehyde, and the triethylamine was omitted. The product was purified by chromatography on silica gel recrystallized from ethyl acetate/ether. Yield: 466 mg (31%). ^{1}H NMR (400MHz, DMSO-d_6): δ 1.01 (t, *J*=7.6 Hz, 3 H), 1.32-1.64 (m, 8 H), 1.70 (s, 6 H), 1.89 (m, 2 H), 2.36 (m, 2 H), 2.58 (m, 2 H), 2.67 (d, *J*=17.6 Hz, 1 H), 3.08 (s, 4 H), 3.29-3.41 (m, 4 H), 3.54 (s, 3 H), 3.83 (m, 4 H), 6.99 (d, *J*=9.3 Hz, 1 H), 7.09 (d, *J*=14.3 Hz, 1 H), 7.35 (t, *J*=8.3 Hz, 1 H), 10.70 (s, 1 H). LC-MS (APCI) calcd for $C_{33}H_{43}FN_4O_4$: 578.33, found (M+H$^+$): 579.40 m/z.

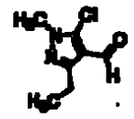
Step 1: 3-Ethyl-1-methyl-1*H*-pyrazol-5-ol



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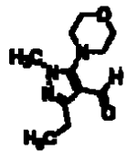
Methylhydrazine (31.5 g, 0.687 mol) in methanol (100 mL) was added dropwise to a solution of ethyl 3-oxopentanoate (100 g, 0.694 mol) in methanol (250 mL) over a period of 45 min, during which time the temperature increased to 45 °C. The reaction mixture was then allowed to stir at room temperature overnight and then evaporated, affording 84.5 g (97%) of the crude title product.

Step 2: 5-Chloro-3-ethyl-1-methyl-1*H*-pyrazole-4-carbaldehyde



$POCl_3$ (236.88 g, 1.543 mol, 144 mL) was added dropwise at 0 °C to DMF (59 g, 0.808 mol). The reaction mixture was then diluted with dichloromethane (200 mL), and 3-ethyl-1-methyl-1*H*-pyrazol-5-ol (84.5 g, from Step 1) was added while stirring at 0 °C. The mixture was refluxed for 3 h and then stirred overnight at room temperature. After this, ice-cold water (500 mL) was added rapidly at 0 °C to the reaction mixture in order to decompose the formylation agent. The organic layer was separated, and the aqueous phase extracted with chloroform several times. The organic layers were then washed with K_2CO_3 solution to obtain a weak alkaline media, dried over Na_2SO_4 and evaporated to give 51.2 g of an oily substance. The residual reaction mass was neutralized with K_2CO_3 to obtain a weak acidic media and extracted with chloroform. The combined extracts were concentrated and the residue purified by chromatography (dichloromethane) on a silica gel to give 71.3 g (62%) of the title product.

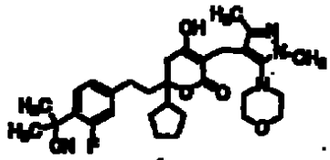
Step 3: 3-Ethyl-1-methyl-5-morpholin-4-yl-1*H*-pyrazole-4-carbaldehyde



Morpholine (35.16 g, 0.4 mol) and water (30 mL) were added under stirring at room temperature to a mixture of 5-chloro-3-ethyl-1-methyl-1*H*-pyrazole-4-carbaldehyde from Step 2 (35 g, 0.202 mol) in HMPA (30 mL). The reaction mixture was heated at 90 °C for 8 h, then diluted with water and extracted with ethyl acetate (3 x 100 mL). The organic extracts were washed with water to obtain a weak alkaline media, dried over Na_2SO_4 and evaporated. The residue was purified by chromatography (hexane/ethyl acetate) on silica gel to afford 37.2 g (82.6%) of the title product. Satisfactory *C,H,N*-analysis was obtained.

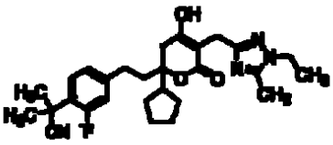
^{1}H NMR (400MHz, DMSO-d_6): δ 1.14 (t, J=7.6 Hz, 3H), 2.71 (q, J=7.6 Hz, 2H), 3.16 (m, 4H), 3.65 (s, 3H), 3.72 (m, 4H), 9.91 (s, 1H). LC-MS (API-ES) calcd for $C_{11}H_{17}N_5O_2$: 223.13, found ($M+H^+$): 224.1 m/z

Example B(49): 2-[4-(2-{2-Cyclopentyl-5-[(1,3-dimethyl-5-morpholin-4-yl-1H-pyrazol-4-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-3-fluorophenyl]-2-methylpropanenitrile



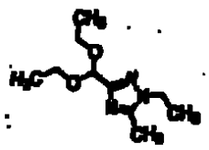
The title compound was prepared analogously to example B(48) where 1,3-dimethyl-5-morpholin-4-yl-1*H*-pyrazole-4-carbaldehyde was substituted in place of 1-methyl-3-(6-methylpyridin-2-yl)-1*H*-1,2,4-triazole-5-carbaldehyde. Yield: 448 (29%). ^{1}H NMR (400MHz, DMSO-d_6): δ 1.22-1.84 (m, 8 H), 1.70 (s, 6 H), 1.90 (m, 2 H), 1.95 (s, 3 H), 2.32 (m, 1 H), 2.58 (m, 3 H), 2.69 (d, J=17.6 Hz, 1 H), 3.04 (m, 4 H), 3.27 (d, J=14.9 Hz, 1 H), 3.30 (d, J=14.9 Hz, 1 H), 3.52 (s, 3 H), 3.82 (m, 4 H), 6.99 (d, J=9.3 Hz, 1 H), 7.09 (d, J=14.3 Hz, 1 H), 7.36 (t, J=8.3 Hz, 1 H), 10.73 (s, 1 H). LC-MS (APCI) calcd for $C_{28}H_{41}FN_4O_4$: 564.31, found ($M+H^+$): 565.40 m/z.

Example B(50): 2-[4-(2-{2-Cyclopentyl-5-[(1-ethyl-5-methyl-1H-1,2,4-triazol-3-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-3-fluorophenyl]-2-methylpropanenitrile



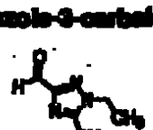
The title compound was prepared analogously to example B(49) where 1-ethyl-5-methyl-1*H*-1,2,4-triazole-3-carbaldehyde (step 2, below) was substituted in place of 1-methyl-3-(6-methylpyridin-2-yl)-1*H*-1,2,4-triazole-5-carbaldehyde, and the triethylamine omitted. Yield = 196 mg (14%). ^{1}H NMR (400MHz, DMSO-d_6): δ 1.15 (t, J=7.3 Hz, 3 H), 1.37-1.71 (m, 14 H), 2.11 (m, 2 H), 2.24 (s, 3 H), 2.40 (m, 1 H), 2.64 (m, 3 H), 2.74 (d, J=17.4 Hz, 1 H), 3.42 (d, J=15.8 Hz, 1 H), 3.52 (d, J=15.8 Hz, 1 H), 3.99 (q, J=7.3 Hz, 2 H), 7.11 (m, 2 H), 7.35 (t, J=8.3 Hz, 1 H), 10.81 (s, 1 H). LC-MS (APCI) calcd for $C_{28}H_{39}FN_4O_3$: 494.27, found ($M+H^+$): 495.30 m/z.

Step 1: 3-Diethoxymethyl-1-ethyl-5-methyl-1*H*-[1,2,4]triazole



To a solution of NaOMe (24 mL, 25% wt in MeOH, 0.105 mol, 4.3 mol%) in MeOH (2.4 L) was added diethoxyacetonitrile (310 g, 2.40 mol), and the reaction mixture was stirred at room temperature for 24 h. The solvent was removed *in vacuo* (300 mbar, 44 °C) and the brown oily residue was dissolved into Et_2O (2.4 L). The organic solution was washed with water (3 x 500 mL) and brine (1 x 400 mL), and dried over Na_2SO_4. The solvent was removed *in vacuo* at 0 °C to yield methyl 2,2-diethoxyethanimidoate (333.52 g, 85%) as a clear liquid. To a solution of NaOMe (25% wt in MeOH, 434 g, 2 mol) and MeOH (2 L), was added ethylhydrazine oxalate (150.14 g, 1 mol), and the mixture was stirred for 10 min. Methyl 2,2-diethoxyethanimidoate (161.2 g, 1 mol) was added, and the mixture was stirred at room temperature for 3 h under a blanket of Nitrogen. The product, (1Z)-2,2-diethoxy-N-ethylethanehydrazonamide was used *in situ*. The crude (1Z)-2,2-diethoxy-N-ethylethanehydrazonamide was treated with acetimidate hydrochloride (109.6 g, 1 mol) and glacial acetic acid (90 g, 1.5 mol), and the mixture was stirred at room temperature for 24 h under nitrogen. LCMS indicated that no reaction had occurred after 24 h. The solvent was removed under vacuum from the reaction mixture and the residue was stored in the freezer. After 8 days the residue was removed from the freezer, warmed to room temperature, and treated with MeOH (1.5 L), acetic Acid (85.7 mL), and acetimidate HCl (98 g, 0.89 mol) from a new bottle, and this mixture was stirred at room temperature for 24 h. LCMS indicated that the starting materials had been consumed and that some of the desired product was present. The solvent was removed *in vacuo* and H_2O (1.5 L) was added to the residue. The mixture was extracted with DCM (5 x 1 L), and the combined organic layers were dried over Na_2SO_4. The solvent was removed under vacuum to afford 168 g of a crude red oil. The product was purified by flash chromatography using 2% MeOH/DMC as eluent (Rf=0.3) affording 58.86 g (29%) of 3-(diethoxymethyl)-1-ethyl-5-methyl-1H-1,2,4-triazole as a red oil, which was 96% pure by ^1H NMR.

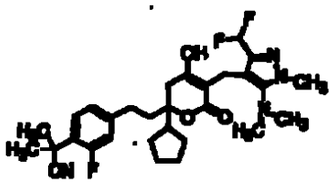
Step 2: 1-Ethyl-5-methyl-1*H*-[1,2,4]triazole-3-carboldehyde



A mixture of 3-(diethoxymethyl)-1-ethyl-5-methyl-1*H*-[1,2,4]triazole from step 1 (58.86g, 0.267 mol) and H_2O (300 mL) was treated slowly with 36% aqueous HCl (55.61 g, 0.534 mol), and the reaction was stirred at room temperature for 24 h. The mixture was

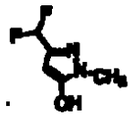
washed with DCM (2 x 200 mL). The aqueous phase was basified to pH 13 with NaOH, and washed with DCM (3 x 200 mL). The combined DCM extracts were discarded. The aqueous phase was neutralized to pH 7 with HCl, and extracted with DCM (3 x 200 mL). The organic phase from this last extraction, containing the product, was dried over Na_2SO_4, and the solvent was removed under vacuum, affording 9.8 g (28%) of 1-ethyl-5-methyl-1*H*-[1,2,4]triazole-3-carbaldehyde which was 98% pure by NMR. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 (t, *J*=7.5 Hz, 3H), 2.51 (s, 3H), 4.20 (q, *J*=7.5 Hz, 2H), 9.91 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.1, 14.9, 44.4, 154.0, 159.2, 184.0. LC-MS (APCI) calcd for $C_5H_7N_3O$: 139.07, found ($M+H^+$): 140.1 m/z. Anal calcd for $C_5H_7N_3O$: C, 51.79; H, 6.52; N, 30.20; Found: C, 51.5; H, 6.36; N, 29.98.

Example B(61): 2-[4-[3-(2-Cyclopentyl-5-[3-(difluoromethyl)-5-(dimethylamino)-1-methyl-1*H*-pyrazol-4-yl]methyl)-4-hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]ethyl]-2-fluorophenyl)-2-methylpropanenitrile



The title compound was prepared analogously to example B(43) where 3-(difluoromethyl)-5-(dimethylamino)-1-methyl-1*H*-pyrazole-4-carbaldehyde (step 3, below) was substituted in place of 1-methyl-3-(6-methylpyridin-2-yl)-1*H*-1,2,4-triazole-5-carbaldehyde, and the triethylamine was omitted. Yield: 142 mg (9%). ^{1}H NMR (400MHz, DMSO-d_6): δ 1.31-1.53 (m, 8 H), 1.70 (s, 6 H), 1.89 (m, 2 H), 2.32 (m, 1 H), 2.57 (m, 3 H), 2.67 (m, 2 H), 2.74 (s, 6 H), 3.40 (d, *J*=15.1 Hz, 1 H), 3.44 (d, *J*=15.1 Hz, 1 H), 3.61 (s, 3 H), 6.98 (d, *J*=8.3 Hz, 1 H), 7.06 (d, *J*=13.1 Hz, 1 H), 7.34 (t, *J*=8.3 Hz, 1 H), 10.92 (s, 1 H). LC-MS (APCI) calcd for $C_{32}H_{40}F_3N_5O_3$: 599.28, found ($M+H^+$): 599.30 m/z.

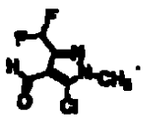
Step 1: 3-(Difluoromethyl)-1-methyl-1*H*-pyrazol-5-ol



To a solution of methyl 4,4-difluoro-3-oxobutanoate (84 g, 0.38 mol) in methanol (500 mL) was added methylhydrazine (20.5 mL, 0.39 mol). The reaction mixture was left to stir overnight at room temperature. The volatiles were removed *in vacuo*, toluene was added (400 mL), the mixture was evaporated again, and this procedure was repeated. The resulting solid residue was purified chromatographically on silica gel using ethyl acetate/dichloromethane

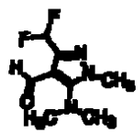
mixture (1:2, R_f = 0.35). The resulting oil was crystallized from ether (200 mL) and dried under the vacuum of a membrane pump (10 mm Hg) for 3 h to give 28 g (49.8%) of the title product.

Step 2: 5-Chloro-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carbaldehyde



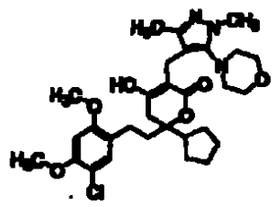
To DMF (40.94 g, 0.56 mol) was added $POCl_3$ (104.4 mL, 1.12 mol) at 0 °C. After 30 min, to the resulting Vilsmier reagent was added 3-(difluoromethyl)-1-methyl-1*H*-pyrazol-5-ol from step 1 above (69.1 g, 0.46 mol), and the mixture was heated at 80 °C for 16 h. Then reaction was diluted with dichloromethane (400 mL), and treated with a solution of potassium carbonate (780 g) in water (2 L) at 0 °C. The organic layer was separated, and the aqueous layer extracted with dichloromethane (3 x 100 mL). The combined organic extracts were washed with water (800 mL), passed through a layer of silica gel (10 x 10 cm), and evaporated. The residue was crystallized from ether (100 mL) and hexane (100 mL) to give 69 g (77%) of the title product.

Step 3: 3-(Difluoromethyl)-5-(dimethylamino)-1-methyl-1*H*-pyrazole-4-carbaldehyde



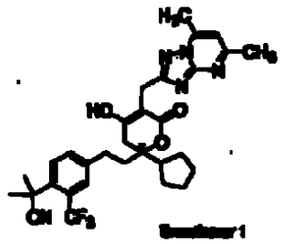
To mixture of 5-chloro-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carbaldehyde (34 g, 0.17 mol) and HMPA (50 mL) was added a 40% aqueous solution of dimethylamine (66.8 mL). The reaction mixture was stirred for at 50 °C for 12 h, diluted with water (1 L), and the product was extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried with sodium sulfate and evaporated. The liquid residue was purified chromatographically on silica gel using dichloromethane/ethyl acetate as eluent (1:2, R_f = 0.25) to give 17.81 g (51.6%) of the title product. Satisfactory *C,H,N*-analysis was obtained. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.93 (s, 6H), 3.72 (s, 6H), 7.07 (t, *J*=56 Hz, 1H), 9.94 (s, 1H). GC-MS calcd for $C_8H_{11}F_2N_3O$: 203.09, found (M^+): 203 m/z.

Example 8(88): 6-[2-(5-Chloro-2,4-dimethoxyphenyl)ethyl]-6-cyclopentyl-9-[(1,3-dimethyl-5-morpholin-4-yl-1H-pyrazol-4-yl)methyl]-4-hydroxy-6,9-dihydro-2H-pyran-2-one



The title compound was prepared analogously to example B(15) using 1,3-dimethyl-5-morpholin-4-yl-1*H*-pyrazole-4-carbaldehyde in place of 2-methyl-5-pyrazin-2-yl-2*H*-[1,2,4]triazole-3-carbaldehyde dihydrochloride monohydrate, and omitting the triethylamine. The yield obtained on a 0.76-mmol scale, was 34 mg (7%). ^{1}H NMR (400MHz, $CDCl_3$): δ 1.18-1.83 (m, 8 H), 2.19 (s, 3 H), 2.28 (m, 1 H), 2.47 (m, 3 H), 2.66 (m, 1 H), 3.07 (m, 2 H), 3.21 (s, 3 H), 3.36 (s, 2 H), 3.69-3.81 (m, 14 H), 6.38 (s, 1 H), 6.94 (s, 1 H). LC-MS (APCI) calcd for $C_{29}H_{39}ClN_6O_5$: 578.26, found ($M+H^+$): 574.20, 576.20 m/z.

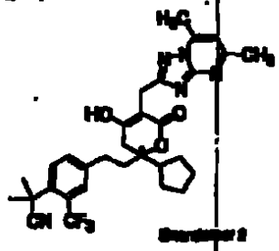
Example B(53): Enantiomer 1 of 2-[4-[2-[2-Cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-2-(trifluoromethyl)phenyl]-2-methylpropanenitrile



Enantiomer 1

The title compound was separated from racemic 2-[4-[2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-2-(trifluoromethyl)phenyl]-2-methylpropanenitrile (338 mg, Example B(29)) using chiral HPLC (Chiralpak AS-H, 140 bar, 50% MeOH). (151.32 mg, 1.84 min retention time, 100% ee).

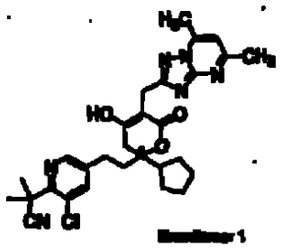
Example B(54): Enantiomer 2 of 2-[4-[2-[2-Cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-2-(trifluoromethyl)phenyl]-2-methylpropanenitrile



Enantiomer 2

The title compound was separated from racemic 2-[4-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-2-(trifluoromethyl)phenyl]-2-methylpropanenitrile (336 mg, Example B(26)) using chiral HPLC (Chiralpak AS-H, 140 bar, 50% MeOH). (239.86 mg, 4.94 min retention time, 100% ee).

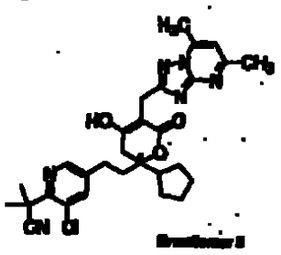
Example B(56): Enantiomer 1 of 2-[3-Chloro-5-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)pyridin-2-yl]-2-methylpropanenitrile



Enantiomer 1

The title compound was separated from racemic 2-[3-chloro-5-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)pyridin-2-yl]-2-methylpropanenitrile (75 mg, Example B(39)) using chiral HPLC (Chiralpak AS-H, 140 bar, 55% MeOH). (11.37 mg, 1.93 min retention time, 91% ee).

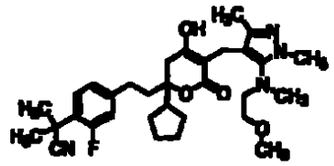
Example B(58): Enantiomer 2 of 2-[3-Chloro-5-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)pyridin-2-yl]-2-methylpropanenitrile



Enantiomer 2

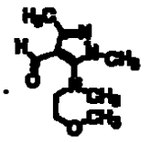
The title compound was separated from racemic 2-[3-chloro-5-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)pyridin-2-yl]-2-methylpropanenitrile (75 mg, Example B(39)) using chiral HPLC (Chiralpak AS-H, 140 bar, 55% MeOH). (9.59 mg, 4.32 min retention time, 98% ee).

Example B(57): 2-(4-[2-[2-Cyclopentyl-4-hydroxy-5-([5-[(2-methoxyethyl)(methyl)amino]-1,2-dimethyl-1H-pyrazol-4-yl]methyl)-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-2-fluorophenyl)-2-methylpropanenitrile



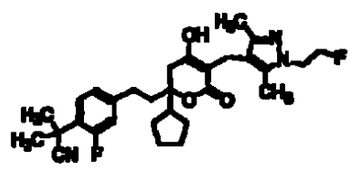
The title compound was prepared analogously to example B(43) where 5-[(2-methoxyethyl)(methyl)amino]-1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde (step 1, below) was substituted in place of 1-methyl-3-(6-methylpyridin-2-yl)-1*H*-1,2,4-triazole-5-carbaldehyde, and the triethylamine was omitted. Yield: 132 mg (9%). ^{1}H NMR (400MHz, DMSO-d_6): δ 1.31-1.70 (m, 14 H), 1.90 (m, 2 H), 1.95 (s, 3 H), 2.32 (m, 1 H), 2.57 (m, 3 H), 2.67 (d, J=17.6 Hz, 1 H), 2.72 (s, 3 H), 3.14 (m, 2 H), 3.21 (s, 3 H), 3.25 (d, J=5.5 Hz, 1 H), 3.31 (m, 3 H), 3.49 (s, 3 H), 6.99 (dd, J=8.2, 1.5 Hz, 1 H), 7.09 (dd, J=13.1, 1.5 Hz, 1 H), 7.35 (t, J=8.4 Hz, 1 H), 10.67 (s, 1 H). LC-MS (APCI) calcd for $C_{32}H_{42}FN_4O_4$: 566.71, found ($M+H^+$): 567.40 m/z.

Step 1: 5-[(2-Methoxyethyl)(methyl)amino]-1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde



A mixture of 2-(methoxyethyl)methylamine (32.93 g, 40 mL, 0.37 mol), 5-chloro-1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde (step 2 of example B(45)) (29.28 g, 0.185 mol), HMPA (25 mL) and water (25 mL) was heated at 120-125 °C for 17 h. The reaction mixture was poured into water (500 mL), and the resulting mixture basified with potassium carbonate. The mixture was extracted with ethyl acetate (5 x 100 mL). The combined organic extracts were washed twice with water, dried with sodium sulfate, filtered, and the solvent removed *in vacuo*. The residue was purified chromatographically on silica gel using hexane/ethyl acetate mixture as eluent, affording 35.35 g (90%) of the title product. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 3H), 2.67 (s, 3H), 3.20 (s, 3H), 3.26 (m, 2H), 3.39 (m, 2H), 3.59 (s, 3H), 9.82 (s, 1H). GC-MS (API-ES) calcd for $C_{10}H_{17}N_3O_2$: 211.13, found ($M+H^+$): 212.1 m/z.

Example B(58): 2-{4-[2-(2-Cyclopentyl-5-{[1-(2-fluoroethyl)-3,5-dimethyl-1H-pyrazol-4-yl]methyl}-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl]-2-fluorophenyl}-2-methylpropanenitrile



The title compound was prepared analogously to example B(43) where 1-(2-fluoroethyl)-3,5-dimethyl-1*H*-pyrazole-4-carbaldehyde (Step 2, below) was substituted in

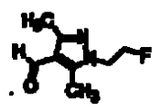
place of 1-methyl-3-(6-methylpyridin-2-yl)-1*H*-1,2,4-triazole-5-carbaldehyde, and the triethylamine was omitted. The product was purified by silica gel chromatography on a Biotage system. Yield: 843 mg (69%). ^{1}H NMR (400MHz, DMSO-d_6): δ 1.30-1.62 (m, 8 H), 1.70 (s, 6 H), 1.84 (m, 2 H), 2.05 (s, 3 H), 2.13 (s, 3 H), 2.27 (m, 1 H), 2.54 (m, 3 H), 2.68 (d, *J*=18.8 Hz, 1 H), 3.14 (d, *J*=14.3 Hz, 1 H), 3.23 (d, *J*=14.3 Hz, 1 H), 4.15 (d, *J*=27.4 Hz, 2 H), 4.81 (d, *J*=47.3 Hz, 2 H), 6.94 (d, *J*=8.0, Hz, 1 H), 7.05 (d, *J*=11.5 Hz, 1 H), 7.34 (t, *J*=8.0 Hz, 1 H), 10.67 (s, 1 H). LC-MS (APCI) calcd for $C_{29}H_{32}F_3N_5O_3$: 555.25, found (MH^+): 556.30 m/z.

Step 1: 1-(2-Fluoroethyl)-3,5-dimethyl-1*H*-pyrazole



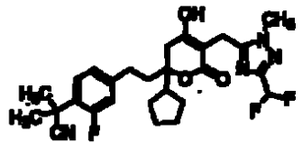
To a suspension of sodium hydride (1.37 mol, (60% in oil) in DMF (350 mL) was added 3,5-dimethyl-1*H*-pyrazole (120 g, 1.25 mol). After this, the reaction mixture was stirred for 1 h at room temperature and treated with 1-bromo-2-fluoroethane (175 g, 1.37 mol) in DMF (200 mL). The reaction mixture was left to stir overnight, diluted with water (2 L), and the product was extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were washed with water (1 L), dried with sodium sulfate, and evaporated. The liquid residue (120 g) was chromatographed on a "Biotage" apparatus with silica gel using ethyl acetate/hexane (1:5) as the eluent (R_f = 0.3) to give 88 g (49.7%) of the title product.

Step 2: 1-(2-Fluoroethyl)-3,5-dimethyl-1*H*-pyrazole-4-carbaldehyde



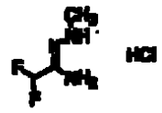
To DMF (58 g, 0.75 mol) was added $POCl_3$ (74.55 mL, 0.8 mol) at 0 °C. After 30 minutes, to the formed Vilsmeier reagent was added 1-(2-fluoroethyl)-3,5-dimethyl-1*H*-pyrazole (88 g, 0.62 mol), and the reaction mixture was heated for 16 h at 80 °C. The reaction mixture was diluted with dichloromethane (400 mL) and treated with potassium carbonate (800 g) in water (2 L) at 0 °C. The organic layer was separated, passed through silica gel (10 x 10 cm), and evaporated. The liquid residue was crystallized from a mixture of hexane (100 mL) and ether (200 mL), separated by filtration, and dried *in vacuo* using an oil pump to give 28.3 g (24.9%) of the title product. Satisfactory *C,H,N*-analysis was obtained. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H), 2.48 (s, 3H), 4.36 (dt, *J*=28 Hz, *J*=5 Hz, 2H), 4.74 (dt, *J*=44 Hz, *J*=5 Hz, 2H), 9.85 (s, 1H). GC-MS calcd for $C_8H_{11}FN_2O$: 170.09, found (M^+): 170 m/z.

Example B(59): 2-{4-[2-(2-Cyclopentyl-5-{3-(difluoromethyl)-1-methyl-1H-1,2,4-triazol-5-yl]methyl}-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl]-3-fluorophenyl}-2-methylpropanenitrile



The title compound was prepared analogously to example B(43) where 3-(difluoromethyl)-1-methyl-1*H*-1,2,4-triazole-5-carbaldehyde (Step 3, below) was substituted in place of 1-methyl-3-(6-methylpyridin-2-yl)-1*H*-1,2,4-triazole-5-carbaldehyde, and the triethylamine was omitted. The product was purified by silica gel chromatography on a Biotage system. Yield: 335 mg (24%). ^{1}H NMR (400MHz, DMSO-d_6): δ 1.20-1.70 (m, 14 H), 1.91 (m, 2 H), 2.27 (m, 1 H), 2.65 (m, 4 H), 3.62 (m, 2 H), 3.85 (s, 3 H), 5.70 (t, *J*=56 Hz, 1 H), 6.99-7.08 (*m*, 2 H), 7.39 (t, *J*=8.3 Hz, 1 H). LC-MS (APCI) calcd for $C_{28}H_{31}F_3N_4O_3$: 516.23, found ($M+H^+$): 517.30 m/z.

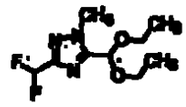
Step 1: 2,2-Difluoro-*N*'-methylethanehydrazonamide Hydrochloride



A stream of dry ammonia was passed through a solution of difluoroacetyl chloride (157 g, 1.37 mol) in ether (1.7 L) cooled to -5 °C in order to obtain an alkaline media. The reaction mixture was then filtered through a 4-cm silica gel layer, eluting with ether (~2.5 L). The ether was evaporated, affording to give 111.4 g (85.5%) of 2,2-difluoroacetamide as a crystalline solid. The 2,2-difluoroacetamide (111.4 g, 1.172 mol) was mixed under ice cooling with phosphorus pentoxide (183 g, 1.289 mol) in a 2-L flask. The flask was equipped with a reflux condenser and heated to 195 °C on an oil bath, in a using a trap cooled with dry ice/acetone mixture to collect 82.8 g (1.075 mol, 91.7%) of 2,2-difluoroacetonitrile. The resulting 2,2-difluoroacetonitrile was cooled to -78 °C and added to a solution of methanol (44.5 mL, 1.1 mol) in ether (400 mL) cooled to -78 °C. The mixture was slowly added under stirring to a solution of HCl (1.188 mol) in ether cooled with dry ice/acetone and the mixture kept at –78 °C for 2 h, then at –20 °C for 24 h, and after that at 0 °C for 24 h. The precipitated crystals were separated by filtration, washed with ether (2 x 500 mL) and vacuum-dried to give 93.5 g (59.8%) of methyl 2,2-difluoroethanimidoate hydrochloride. Methylhydrazine (34.5 mL, 0.649 mol) was added under an atmosphere of Ar to a solution of methyl 2,2-difluoroethanimidoate hydrochloride (93.5 g, 0.6425 mol) in methanol (300 mL), and the mixture was stirred at room temperature for 4 days. The reaction mixture was then diluted

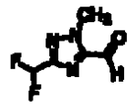
with ethyl acetate, causing a partial crystallization of a hydrochloride salt. The crystals (12 g) were separated by filtration, and the mother liquors evaporated to give an additional quantity of product. The combined yield of crude 2,2-difluoro-*N*-methylethanehydrazonamide hydrochloride was 104.9 g (0.6206 mol, 99.6%) yield. The compound was found to be 83% area% pure by LC/MS and was used without further purification.

Step 2: 5-(Diethoxymethyl)-3-(difluoromethyl)-1-methyl-1*H*-1,2,4-triazole



A solution of diethoxyacetonitrile (75 g, 0.579 mol) in methanol (210 mL) was added at room temperature to a solution of sodium methoxide (28.3 g, 0.522 mol) in methanol (460 mL). The mixture was stirred overnight, and then methanol was evaporated. The residue was diluted with dichloromethane (200 mL) and water (300 mL). The organic layer was separated, and the aqueous one was extracted with dichloromethane (2 x 150 mL). The combined organic layer was dried over Na_2SO_4, and evaporated to give 85 g of crude methyl 2,2-diethoxyacetimidate (~90% yield). A solution of methyl 2,2-diethoxyacetimidate prepared above (0.6206 mol, 125.1 g of 60% purity) in methanol (300 mL) was added to a solution of 2,2-difluoro-*N*-methylethanehydrazonamide hydrochloride (0.6206 mol, obtained in Step 1) in methanol (700 mL). Anhydrous sodium acetate (61.1 g, 0.745 mol) was added, and the mixture was stirred at 30 °C for 3 days. The reaction mixture was then evaporated, and the residue subjected to chromatography (ethyl acetate/hexane 1:4 → 1:1) on a silica gel column, followed by vacuum distillation to give 47.6 g (32.8%) of 5-(diethoxymethyl)-3-(difluoromethyl)-1-methyl-1*H*-1,2,4-triazole.

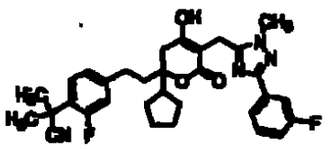
Step 3: 3-(Difluoromethyl)-1-methyl-1*H*-1,2,4-triazole-5-carbaldehyde



Water (180 mL) was added to 5-(diethoxymethyl)-3-(difluoromethyl)-1-methyl-1*H*-1,2,4-triazole (47.6 g, 0.203[illegible] mol, from Step 2), and the mixture was degassed. Then concentrated HCl (73 mL; 0.81 mol, 11.1 M) was added, and the mixture was stirred at 55-60 °C for 24 h. After this, the reaction mixture was evaporated, and the residue was repeatedly (8-10 times) evaporated with THF until the water and HCl were completely removed. The final residue was distilled under vacuum to give the crude title product (bp 46-50 °C at 0.04 mm Hg), containing, according to LC-MS data, 7% of a dimerization side-product. Further purification on a silica gel (ethyl acetate/hexane 1:3) yielded 18.37 g (56.3%) of 3-(difluoromethyl)-1-methyl-1*H*-1,2,4-triazole-5-carbaldehyde. Satisfactory *C,H,N*-analysis was

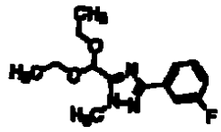
obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.25 (s, 3H), 6.74 (t, J=56 Hz, 1H), 10.01 (s, 1H). LC/MS (API-ES) calcd for $C_9H_6F_2N_2O$: 181.04, found ($M+H^+$): 182.1; ($M+18+H^+$): 199.1 m/z.

Example B(60): 2-{4-[2-(2-Cyclopentyl-5-{[3-(3-fluorophenyl)-1-methyl-1H-1,2,4-triazol-5-yl]methyl}-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl]-2-fluorophenyl}-2-methylpropanenitrile



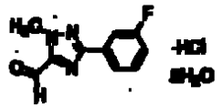
The title compound was prepared analogously to example B(43) where 3-(3-fluorophenyl)-1-methyl-1*H*-1,2,4-triazole-5-carbaldehyde hydrochloride dehydrate (Step 2, below) was substituted in place of 1-methyl-3-(6-methylpyridin-2-yl)-1*H*-1,2,4-triazole-5-carbaldehyde. The product was purified by silica gel chromatography on a Biotage system. Yield: 280 mg (17%). ^{1}H NMR (400MHz, DMSO-d_6): δ 1.36-1.70 (m, 14 H), 2.04 (m, 2 H), 2.42 (m, 1 H), 2.63 (m, 3 H), 2.75 (d, J=19.8 Hz, 1 H), 3.65 (d, J=15.8 Hz, 1 H), 3.74 (d, J=15.8 Hz, 1 H), 3.89 (s, 3 H), 6.99 (d, J=7.8 Hz, 1 H), 7.09-7.20 (m, 3 H), 7.35 (m, 1 H), 7.48 (d, J=8.8 Hz, 1 H), 7.64 (d, J=8.1 Hz, 1 H), 11.18 (s, 1 H). LC-MS (APCI) calcd for $C_{32}H_{36}F_2N_4O_3$: 560.28, found ($M+H^+$): 561.30 m/z.

Step 1: 5-(Diethoxymethyl)-3-(3-fluorophenyl)-1-methyl-1*H*-1,2,4-triazole



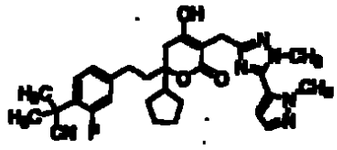
MeONa (2.35 g, 41 mmol) was added to a stirred solution of 3-fluorobenzonitrile (50.0 g, 413 mmol) in methanol (300 mL). The mixture was stirred at room temperature for 3 days and concentrated *in vacuo*. The residue was dissolved in ether (300 mL), washed with water (2 x 150 mL), brine (150 mL), dried with Na_2SO_4, and concentrated *in vacuo* to afford 62.8 g (99%) of methyl 3-fluorobenzenecarboximidoate. Methylhydrazine (21.8 mL, 410n mmol) was added to a stirred solution of methyl 3-fluorobenzenecarboximidoate (62.8 g, 410 mmol) in THF (350 mL). The mixture was stirred at room temperature for 3 days, then. Then methyl 2,2-diethoxyethanimidoate (68.1 g, 410 mmol) and acetic acid (37.5 mL, 656 mmol) were added. The mixture was stirred for 24 h. The reaction was diluted with CH_2Cl_2 (500 mL), and the formed precipitate was filtered off. The filtrate was washed with 10% citric acid (2 x 200 mL), water (300 mL), brine (200 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to flash chromatography on silica gel using 1% MeOH/$CHCl_3$ as eluent to give 24.0 g (21%) of the title product.

Step 2: 3-(3-Fluorophenyl)-1-methyl-1*H*-1,2,4-triazole-5-carbaldehyde hydrochloride dihydrate



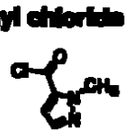
A solution of 5-(diethoxymethyl)-3-(3-fluorophenyl)-1-methyl-1*H*-1,2,4-triazole (24.0 g, 88 mmol) in 4M HCl (88 mL) was stirred at 80 °C for 2 h. The mixture was concentrated *in vacuo*, and the residue was recrystallized from MeOH/Et_2O mixture (1:1). The resulting solvate was dissolved in water/THF (1:2) and concentrated *in vacuo* to dryness to afford 11.33 g (47%) of the title product. Satisfactory *C,H,N*-analysis was obtained. ^1H NMR (400 MHz, D_2O+TFA): δ 4.16 (s, 3H), 8.47 (s, 1H), 7.42 (m, 1H), 7.62 (m, 1H), 7.70 (m, 1H), 7.77 (m, 1H). LC/MS (API-ES) calcd for $C_{10}H_8FN_3O$: 205.07, found ($M+H^+$): 206.0; ($M+18+H^+$): 224.0 m/z.

Example B(51): 2-{4-[2-(2-Cyclopentyl-4-hydroxy-5-{[1-methyl-5-(1-methyl-1H-pyrazol-5-yl)-1H-1,2,4-triazol-3-yl]methyl}-6-oxo-5,6-dihydro-2H-pyran-2-yl)ethyl]-2-fluorophenyl}-2-methylpropanenitrile



The title compound was prepared analogously to example B(43) where 1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-1,2,4-triazole-3-carbaldehyde (Step 3, below) was substituted in place of 1-methyl-3-(6-methylpyridin-2-yl)-1*H*-1,2,4-triazole-5-carbaldehyde, and the triethylamine omitted. The product was purified by silica gel chromatography on a Biotage system. Yield: 67 mg (4 %). ^1H NMR (400MHz, DMSO-d_6): δ 1.36-1.70 (m, 14 H), 2.07 (m, 2 H), 2.34 (m, 2 H), 2.63 (m, 3 H), 3.46-3.57 (m, 2 H), 3.74 (s, 3 H), 3.84 (s, 3 H), 6.76(s, 1 H), 7.01-7.22 (m, 3 H), 7.59 (s, 1 H). LC-MS (APCI) calcd for $C_{32}H_{38}FN_6O_3$: 548.28, found ($M+H^+$): 547.30 m/z.

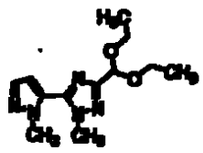
Step 1: 1-Methyl-1*H*-pyrazole-5-carbonyl chloride



To a stirred solution of 1-methyl-1*H*-pyrazole (77.0 g 0.916 mol) in absolute ether (900 mL) under an atmosphere of argon was added a 1.6 M solution of *n*-BuLi in hexane (600 mL, 0.96 mol) dropwise at -40 °C over a period of 2 h. The reaction mixture was stirred at this temperature for a further 1 h, then siphoned into a mixture of solid carbon dioxide with ether. After heating to room temperature, the resulting mass was treated with water (1.5 L), the aqueous layer was separated, washed with ether (500 mL), concentrated to half volume under

reduced pressure on a rotary evaporator, cooled to 2-3 °C, and acidified while stirring with concentrated HCl to pH = 3. The resulting precipitate was separated by filtration, washed with ice-cold water (25 mL), dried first in open air, and then in a vacuum desiccator over P_2O_5 to give 86.5 g (76%) of 1-methyl-1*H*-pyrazole-5-carboxylic acid as a white powder. To thionyl chloride (350 mL) was added 1-methyl-1*H*-pyrazole-5-carboxylic acid (86.5 g, 0.67 mol) in portions over a 35 min period, such that each portion was consumed before addition of the next. After this, the reaction mixture was refluxed for 4.5 h. The excess thionyl chloride was removed under vacuum at a bath temperature below 35 °C. The residue was subjected to vacuum fractional distillation through a 15-cm Vigreux column. A fraction boiling at 71-72 °C at 15-16 mm Hg was collected to obtain the title product (49.0 g, 51%) as a colorless liquid.

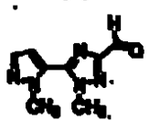
Step 2: 3-(Diethoxymethyl)-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-1,2,4-triazole



To a stirred solution of diethoxyacetonitrile (60 g, 0.465 mol) in absolute methanol (150 mL) under an atmosphere of argon was added a solution of sodium methylate (2.5 g; 0.047 mol) in absolute methanol (20 mL), and the reaction mixture was stirred at room temperature until the nitrile disappeared completely (70-75 h). The reaction was monitored by ^{1}H NMR. The reaction mixture was treated, while stirring, with CO_2 until the precipitate of sodium carbonate ceased to form. The latter was filtered off and washed with methanol (50 mL). The filtrate was evaporated under on a rotary evaporator at a bath temperature less than 30 °C. The resulting liquid was dissolved in ether (250 mL), filtered to remove the remaining inorganic salts, and evaporated again to give the crude methyl 2,2-diethoxyethanimidoate (71.0 g, 95%). It was distilled under vacuum through a 15-cm Vigreux column, affording 56.2 g (75%) of methyl 2,2-diethoxyethanimidoate (bp. 77-78 °C at 20-22 mm Hg) with a purity of more than 95% by ^{1}H NMR. To a solution of the methyl 2,2-diethoxyethanimidoate (52.1 g, 0.321 mol) and triethylamine (49 mL, 0.353 mol) in absolute THF (300 mL) was added a solution of 1-methyl-1*H*-pyrazole-5-carbonyl chloride (46.5 g, 0.321 mol, from Step 1) in absolute THF (150 mL) dropwise under an atmosphere of argon at 0-5 °C over a period of 2 h. The reaction mixture was stirred overnight at a room temperature. The residue the formed was filtered off, and the filtrate was evaporated on a rotary evaporator to give methyl (1*Z*)-2,2-Diethoxy-*N*-[(1-methyl-1*H*-pyrazol-5-yl)carbonyl]ethanimidoate (90 g) as a yellow viscous mass, which was used at the next stage without additional purification. The 90 g of the crude product *N*-acylated imidate ester obtained at the previous stage was dissolved in absolute

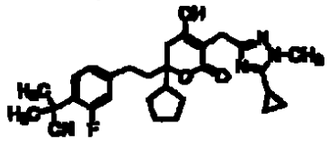
dichloromethane (450 mL), and treated with methylhydrazine (17.1 mL, 0.321 mol) with stirring over a period of 10 min. The reaction mixture was stirred at room temperature for 3 h, washed with water (3 x 300 mL), and dried with anhydrous sodium sulfate. The solvent was removed under vacuum on a rotary evaporator, and the residue (58.5 g) was purified chromatographically on silica gel using hexane/ethyl acetate (1:2) as the eluent. The solvent was evaporated to give 40.1 g (47% based on 1-methyl-1*H*-pyrazole-5-carbonyl chloride) of the pure title product.

Step 2: 1-Methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-1,2,4-triazole-3-carbaldehyde



To a 4 N solution of HCl (185 mL, 0.74 mol) was added 3-(diethoxymethyl)-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-1,2,4-triazole (40.1 g, 0.151 mol), and the reaction mixture was left to stir overnight. To the resulting mixture was added potassium carbonate (185 g) in portions under vigorous stirring, and the resulting mixture was extracted with ethyl acetate (5 x 300 mL). The organic layer was dried with anhydrous sodium sulfate, and the solvents were removed under vacuum on a rotary evaporator. To the residue was added absolute ether (4 x 100 mL) to give 27.3 g (94.5%) of the title product as a light-beige powder. Satisfactory *C,H,N*-analysis was obtained. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.04 (s, 3H), 4.06 (s, 3H), 6.98 (d, *J*=2 Hz, 1H), 7.67 (d, *J*=2 Hz, 1H), 9.95 (s, 1H). LC/MS (API-ES) calcd for $C_6H_7N_5O$: 191.08, found ($M+H^+$): 192.0 m/z.

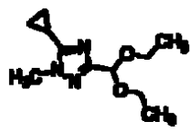
Example B(62): 3-[4-(2-{2-Cyclopentyl-6-[(5-cyclopropyl-1-methyl-1H-1,2,4-triazol-3-yl)methyl]-4-hydroxy-5-oxo-5,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile



The title compound was prepared analogously to example B(43) where 5-cyclopropyl-1-methyl-1H-[1,2,4]triazole-3-carbaldehyde (Step 2, below) was substituted in place of 1-methyl-3-(6-methylpyridin-2-yl)-1*H*-1,2,4-triazole-5-carbaldehyde, and the triethylamine omitted. The product was purified by silica gel chromatography on a Biotage system. Yield: 326 mg (23 %). ^{1}H NMR (400MHz, DMSO-d_6): δ 0.70 (m, 2 H), 0.90 (m, 2 H), 1.36-1.71 (m, 14 H), 1.97-2.12 (m, 3 H), 2.39 (m, 1 H), 2.52 (d, *J*=15.8 Hz, 1 H), 2.63 (m, 2 H), 2.72 (d, *J*=15.8 Hz, 1 H), 3.37 (d, *J*=15.8 Hz, 1 H), 3.47 (d, *J*=15.8 Hz, 1 H), 3.85 (s, 3 H), 7.10 (m, 2

H), 7.37 (t, J=6.3 Hz, 1 H), 10.70 (s, 1 H). LC-MS (APCI) calcd for $C_{28}H_{30}FN_5O_3$: 503.27, found ($M+H^+$): 507.30 m/z.

Step 1: 5-Cyclopropyl-3-diethoxymethyl-1-methyl-1*H*-[1,2,4]triazole



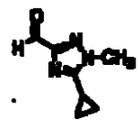
Cyclopropanecarbonitrile (100 g, 1.49 mol), methanol (59.7 g, 76 mL, 1.86 mol), and diethyl ether (184 mL) were charged to a 2 L three-necked flask. The mixture was cooled to -10 °C while stirring and HCl (g) (232 g, 6.36 mol) was then bubbled through the mixture solution such that the internal temperature was maintained below -5 °C. Upon completion of gas addition, the mixture was stirred for 1.5 h at -10 °C. Ether (885 mL) was added slowly over a 1-h period while continuing to maintain a the temperature below 0 °C. The resulting solids were filtered and rinsed with diethyl ether (3 x 300 mL). The solids were further dried under vacuum, affording 181.5 g (89.8 % yield) of methyl cyclopropanecarboximidoate hydrochloride. mp: 112-114 °C

In a 2 L three-neck flask, a solution of diethoxyacetonitrile (125 g , 968 mmol) in methanol (300 mL, anhydrous) was treated with a 25 wt % solution of sodium methoxide (21.0 g, 389 mmol) in methanol, producing a slightly exothermic reaction. After cooling, the mixture was stirred at room temperature for 15 h. Upon completion of the reaction, the solvent was slowly evaporated under vacuum. The remaining brown-colored residue was solvated with diethyl ether (1 L), then washed with water (3 x 500 mL), followed by brine (1 x 200 mL). The organic layer was dried using magnesium sulfate, the salts filtered, and the solvent evaporated carefully under vacuum to afford 192 g (85 % yield) of methyl 2,2-diethoxyethanimidoate as a colorless liquid.

Methyl 2,2-diethoxyethanimidoate (39.0 g, 242 mmol) was dissolved in tetrahydrofuran (345 mL), mixed with methylhydrazine (11.1 g, 242 mmol), then the mixture stirred at room temperature for 5 h, at which point LC/MS analysis confirmed the formation of the amidrazone intermediate. Methyl cyclopropanecarboximidoate hydrochloride (32.8 g, 242 mmol) was added to the reaction mixture, resulting in a suspension. Acetic acid (21.8 g, 363 mmol) was added slowly to the suspension, and the resulting exothermic reaction controlled with a cooling bath. After addition was completed, the reaction mixture was stirred at ambient temperature overnight. After LC/MS analysis indicated that the starting reactants had been consumed, the mixture was diluted with dichloromethane (500 mL) and stirred for 1 h. The solids were filtered and rinsed with dichloromethane (3 x 200 mL), and the filtrate concentrated *in vacuo*. The remaining oil was purified by column chromatography on silica gel

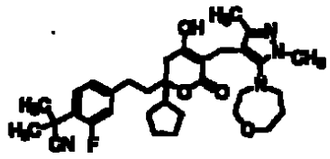
(mobile phase: ethyl acetate, then with 1, 3, 5, 10% methanol, consecutively). The product-containing fractions were pooled and the solvent evaporated *in vacuo*. After further drying under high vacuum, 27.4 g of the title acetal was obtained as an oil containing 12.4 weight % of ethyl acetate as an impurity.

Step 2: 5-Cyclopropyl-1-methyl-1*H*-[1,2,4]triazole-3-carbaldehyde



In a 2 L round-bottomed flask containing the crude 5-cyclopropyl-3-(diethoxymethyl)-1-methyl-1*H*-1,2,4-triazole from Step 2, a solution of 2 N HCl (125 mL) was added and the reaction was allowed to stir at room temperature for 23 h, at which point, LC/MS analysis confirmed the formation of the aldehyde. The mixture was then treated with solid sodium hydroxide until a pH of 13 was obtained. The aqueous mixture was extracted with dichloromethane (3 x 150 mL), and the combined organic layers dried over sodium sulfate, filtered and the solvent evaporated under vacuum. The crude material was distilled Kugel-Rhor distillation at 135 °C- 146 °C to afford 11.4 g (61.9 %) the title product as a yellow-colored oil. This material contained 4.8 wt % of the self-condensed side-product, 3,5-dicyclopropyl-1-methyl-1H-1,2,4-triazole, by ^{1}H NMR. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98 (m, 2H), 1.10 (m, 2H), 2.22 (m, 1H), 4.00 (s, 3H), 9.78 (s, 1H). LC/MS (APCI) calcd for $C_7H_9N_3O$: 151.07, found ($M+H^+$): 152.1 m/z.

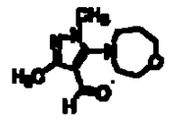
Example B(63): 2-(4-[2-(3-Cyclopentyl-5-[1,3-dimethyl-5-(1,4-oxazepan-4-yl)-1H-pyrazol-4-yl]methyl}-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl]-2-fluorophenyl}-2-methylpropanenitrile



The title compound was prepared analogously to example B(43) where 1,3-dimethyl-5-(1,4-oxazepan-4-yl)-1*H*-pyrazole-4-carbaldehyde (step 1, below) was substituted in place of 1-methyl-3-(6-methylpyridin-2-yl)-1*H*-1,2,4-triazole-5-carbaldehyde, and the triethylamine omitted. The product was purified by silica gel chromatography on a Biotage system. Yield: 553 mg (35 %). ^{1}H NMR (400MHz, DMSO-d_6): δ 1.32-1.64 (m, 8 H), 1.70 (s, 6 H), 1.82 (m, 2 H), 1.89 (m, 2 H), 1.94 (s, 3 H), 2.32 (m, 1 H), 2.57 (m, 3 H), 2.88 (d, J=17.6 Hz, 1 H), 3.17-3.27 (m, 6 H), 3.52 (s, 3 H), 3.64 (m, 2 H), 3.78 (t, J=5.8 Hz, 2 H), 6.99 (d, J=8.1 Hz, 1 H),

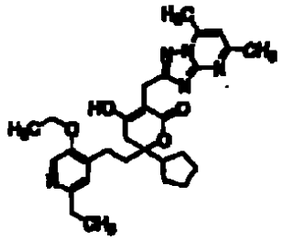
7.06 (d, J=13.1 Hz, 1 H), 7.35 (t, J=8.6 Hz, 1 H), 10.69 (s, 1 H). LC-MS (APCI) calcd for $C_{20}H_{22}FN_3O_4$: 579.38, found ($M+H^+$): 579.40 m/z.

Step 2: 1,3-Dimethyl-5-(1,4-oxazepan-4-yl)-1*H*-pyrazole-4-carbaldehyde



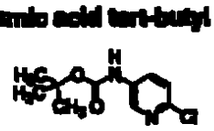
Homomorpholine hydrochloride (28.2 g, 200 mol) was added to a mixture of 5-chloro-1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde (21.66 g, 0.1366 mol, Example B(45), Step 2), HMPA (30 mL), water (50 mL), and potassium carbonate (59 g, 0.6 mol) at constant stirring and room temperature. The reaction mixture was heated at 80 °C for 50 h, diluted with water, and extracted with ethyl acetate (3 x 100 mL). The organic extracts were washed with water to weakly alkaline pH and dried with sodium sulfate. The product was purified chromatographically using *hexane/ethyl acetate* mixture as eluent to afford the title product (18.7 g, 61%). Satisfactory *C,H,N*-analysis was obtained. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.91 (m, 2H), 2.27 (s, 3H), 3.33 (m, 4H, overlap with H_2O peak), 3.62 (s, 3H), 3.72 (m, 2H), 3.81 (m, 2H), 9.83 (s, 1H). LC/MS (API-ES) calcd for $C_{11}H_{17}N_3O_2$: 223.13, found ($M+H^+$): 224.1 m/z.

Example B(94): 6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one



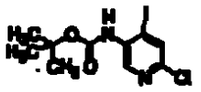
The title compound was prepared analogously to example A(1) where 6-cyclopentyl-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]dihydro-2*H*-pyran-2,4(3*H*)-dione from step 8 below was substituted in *place of* 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.19 (t, J=7.6 Hz, 3 H), 1.31 (t, J=6.8 Hz, 3 H), 1.40-1.78 (br m, 8 H), 2.03-217 (m, 2 H), 2.48-2.72 (m, 12 H), 2.85 (d, J=17.4 Hz, 1 H), 3.76 (d, J=16.4 Hz, 1 H), 3.87 (d, J=16.2 Hz, 1 H), 4.08 (m, 2 H), 7.09 (m, 2 H), 8.13 (s, 1 H), 10.96 (s, 1 H). MS (ESI): 520.20 $(M+H)^+$

Step 1: (5-Chloro-pyridin-3-yl)-carbamic acid tert-butyl ester



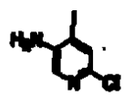
Di-tert-butyldicarbonate (41 g, 0.19 mol) was added to a solution of 5-amino-2-chloropyridine (20 g, 0.16 mol) dissolved in 1,4-dioxane (120 mL). The reaction mixture was heated to reflux for 16 hours. The reaction was cooled to room temperature and poured into H_2O and extracted with ether. The organics were dried over Na_2SO_4 and concentrated to a residue. Trituration with hexanes gave the product as a tan solid (31 g, 85%). ^1H NMR (400MHz, $CDCl_3$): δ 1.52 (s, 9 H), 6.58 (s, 1 H), 7.26 (d, J=8.6 Hz, 1 H), 7.96 (m, 1 H), 8.23 (d, J=2.8 Hz, 1 H).

Step 2: (6-Chloro-4-iodo-pyridin-3-yl)-carbamic acid tert-butyl ester



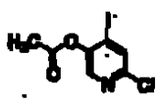
n-BuLi (52.4 mL, 0.12 mol, 2.5 M soln in hexanes) was added dropwise over 30 mins to a cooled -78 °C solution of (6-chloro-pyridin-3-yl)-carbamic acid tert-butyl ester (10.0 g, 43.7 mmol) and TMEDA (18.8 mL, 0.13 mol) dissolved in ether. The solution was warmed to -10 °C, stirred for 2 hours and then recooled to -78 °C. A solution of iodine (22.75 g, 90 mmol) in ether (100 mL) was added via an addition funnel and the reaction was warmed to room temperature and stirred for 16 hours. The reaction was quenched with sat NH_4Cl and sodium thiosulfite was added. The mixture was stirred for 30 mins and then extracted with ether. The organic extracts were washed with sodium thiosulfite, dried over $MgSO_4$, filtered and concentrated. Purification by silica gel chromatography (0% to 15% EtOAc in hexanes) gave the product (8.6 g, 55%). ^1H NMR (300MHz, $CDCl_3$): δ 1.52 (s, 9 H), 6.58 (s, 1 H), 7.26 (d, J=8.6 Hz, 1 H), 7.96 (m, 1 H), 8.23 (d, J=2.8 Hz, 1 H).

Step 3: 6-Chloro-4-iodo-pyridin-3-ylamine



A solution of (6-chloro-4-iodo-pyridin-3-yl)-carbamic acid tert-butyl ester (8.6 g, 24.3 mmol) dissolved in CH_2Cl_2 was treated with 4 N HCl/dioxane (100 mL) and stirred at room temperature for 2 hours. The reaction mixture was diluted with CH_2Cl_2 and washed with 2 N NaOH. The organic layer was dried over $MgSO_4$ and concentrated to give the product as a solid (6.2 g, 100%).

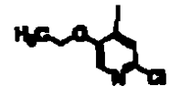
Step 4: Acetic acid 6-chloro-4-iodo-pyridin-3-yl ester



Boron trifluoride diethyl etherate (6.2 mL, 48.9 mmol) was slowly added to a cooled -15 °C solution of 6-chloro-4-iodo-pyridin-3-ylamine (5.82 g, 22.9 mmol) dissolved in DME (98

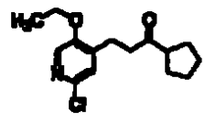
mL) and CH_2Cl_2 (12 mL). Tert-butyl nitrite (3.6 mL, 27.6 mmol) was slowly added maintaining the temperature below -5 °C. The reaction was stirred at -10 °C for 25 minutes and then at 0 °C for 20 minutes. The mixture was diluted with pentanes (100 mL) and the tetrafluoroborate diazonium salt was collected by filtration. The salt was dissolved immediately by dissolving it in acetic anhydride (20 mL) and heated to 95 °C for 2 hours. The reaction was cooled to room temperature and partitioned between diethyl ether and saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated. Purification by silica gel chromatography (0% to 60% EtOAc in hexanes) gave the product as a white solid (3.34g, 49%). ^1H NMR (300MHz, $CDCl_3$): δ 2.40 (s, 3 H), 7.82 (s, 1 H), 8.09 (s, 1 H).

Step 5: 2-Chloro-5-ethoxy-4-iodo-pyridine



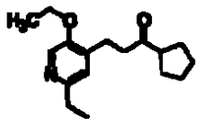
A mixture of acetic acid 6-chloro-4-iodo-pyridin-3-yl ester (3.58 g, 12.1 mmol), potassium carbonate (0.83 g, 6.0 mmol) in MeOH (20 mL) was stirred for 90 minutes. The solvent was removed in vacuuo and the residue was partitioned between ether and 1 N citric acid. The organic layer was dried over $MgSO_4$ and concentrated to give an off white solid (2.86 g, 95%). The solid was dissolved in DMF (20 mL) and treated with potassium carbonate (4.83 g, 34 mmol) followed by ethyl iodide (2.73 mL, 33.6 mmol). The reaction mixture was heated to 60 °C for 2 hours and then cooled to room temperature. The mixture was poured into 20% citric acid and extracted with ether. The ether extracts were washed with H_2O, brine, dried over $MgSO_4$ and concentrated. Purification by silica gel chromatography (0% to 60% EtOAc in hexanes) gave the compound as a white solid (3 g, 95%). ^1H NMR (300MHz, $CDCl_3$): δ 1.51 (t, J=7.0 Hz, 3 H), 4.17 (q, J=7.0 Hz, 2 H), 7.74 (s, 1 H), 7.81 (s, 1 H).

Step 6: 3-(2-Chloro-5-ethoxy-pyridin-4-yl)-1-cyclopentyl-propan-1-one



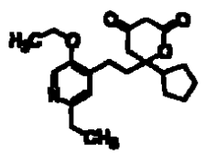
A mixture of 2-chloro-5-ethoxy-4-iodo-pyridine (1.5 g, 5.3 mmol), 1-cyclopentyl-2-propen-1-ol (0.83 g, 6.61 mmol), sodium acetate (0.54 g, 6.6 mmol), palladium (II) acetate (24 mg, 0.11 mmol) in DMAC (10 mL) was heated to 90 °C under N_2 for 16 hours. The reaction mixture was partitioned between 1N HCl and EtOAc. The organic layers were washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated. Purification by silica gel chromatography (0% to 60% EtOAc in hexanes) gave the desired product (1.2g, 58%). ^1H NMR (300MHz, $CDCl_3$): δ 1.44 (t, J=7.0 Hz, 3 H), 1.55-1.87 (m, 8 H), 2.75 (m, 2 H), 2.88 (m, 3 H), 4.11 (q, J=7.0 Hz, 2 H), 7.09 (s, 1 H), 7.89 (s, 1 H).

Step 7: 1-Cyclopentyl-3-(5-ethoxy-2-ethyl-pyridin-4-yl)-propan-1-one



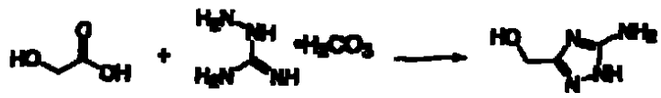
A solution of 3-(2-chloro-5-ethoxy-pyridin-4-yl)-1-cyclopentyl-propan-1-one (1.2 g, 4.3 mmol) dissolved in DMF (10 mL) was treated with potassium carbonate (0.88 g, 6.4 mmol), tetrakis(triphenylphosphine)palladium (0.12 g, 0.11 mmol), and triethylborane (4.5 mL, 4.5 mmol). The reaction was heated to 150 °C for 2 hours. The reaction was quenched with 1 N HCl and then made basic with 2 N NaOH. The mixture was extracted with ether and the organic layers were dried over $MgSO_4$ and concentrated. Purification by silica gel chromatography (0% to 60% EtOAc in hexanes) gave the product (0.8 g, 68%). ^1H NMR (300MHz, $CDCl_3$): δ 1.25 (t, J=7.6 Hz, 3 H), 1.42 (t, J=6.9 Hz, 3 H), 1.55-1.87 (m, 8 H), 2.73 (m, 4 H), 2.85 (m, 3 H), 4.11 (q, J=6.9 Hz, 2 H), 6.83 (s, 1 H), 8.08 (s, 1 H).

Step 8: 6-Cyclopentyl-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]dihydro-2*H*-pyran-2,4(3*H*)-dione



Methyl acetoacetate (1.2 mL, 10.9 mmol) was added to a cooled -60 °C suspension of LDA [prepared from diisopropylamine (3.0 mL, 21.8 mmol), and n-BuLi (8.7 mL, 21.8 mmol) dissolved in THF (30 mL)]. The reaction was stirred for 30 mins and then a solution of 1-cyclopentyl-3-(5-ethoxy-2-ethyl-pyridin-4-yl)-propan-1-one (1.0 g, 3.6 mmol) dissolved in THF (30 mL) was added. The reaction was warmed to room temperature and stirred for 2 hours. The reaction was poured into 1 N NaOH and extracted with EtOAc. The organic layers were dried over $MgSO_4$ and concentrated. The residue was dissolved in methanol (100 mL), treated with potassium carbonate (1.5 g, 10.9 mmol), and refluxed under N_2 for 120 mins. The reaction mixture was partitioned between H_2O and IPE. The aqueous layer was made neutral with 1N HCl and extracted with EtOAc. The organic layers were dried over $MgSO_4$ and concentrated to give the product (1.3 g, 99% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J=7.6 Hz, 3 H), 1.43 (t, J=6.8 Hz, 3 H), 1.50-2.05 (br m, 9 H), 2.34 (m, 2 H), 2.62-2.77 (m, 6 H), 3.44 (m, 2 H), 4.11 (q, J=6.8 Hz, 2 H), 6.90 (s, 1 H), 8.08 (s, 1 H).

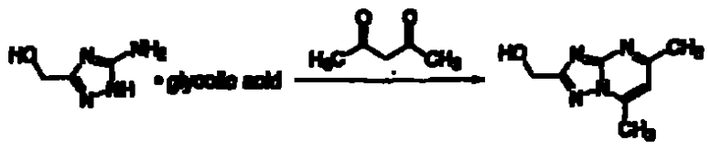
Example (C1): Preparation of the glycolate salt of (5-amino-1*H*-1,2,4-triazol-3-yl)methanol



glycolate salt

Glycolic acid (1 L, 70% in water, 11.51 mol) was added to a 5 L flask. To the solution was slowly added aminoguanidine bicarbonate (783.33 g, 5.755 mol) in portions to control significant bubbling. As solids are added, the solution cools due to endothermic dissolution. The solution was gently heated to maintain an internal temp of 25 °C during addition. Ten minutes after complete addition of aminoguanidine bicarbonate, conc. nitric acid (6.8 mL) was carefully added. The solution was heated to an internal temperature of 104-108 °C (mild reflux) for 22 h. The heating was discontinued and the solution allowed to cool, with stirring. At an internal temp of ~81 °C, solids began to crystallize. After the internal temperature was just below 80 °C, ethanol (absolute, 375 mL) was slowly added to the mixture. After the internal temp had cooled to ~68 °C, the cooling was sped up by the use of an ice/water bath. After cooling below rt, the solution became very thick but remained stirrable at all times. The slurry was stirred for 2h at T<10 °C, then filtered and the solids rinsed with ethanol (900 mL cold, then 250 mL rt). The solids were dried overnight in a vacuum oven (~25 mmHg, 45-50 °C) to provide 815.80 g (75%) of (5-amino-1*H*-1,2,4-triazol-3-yl)methanol as the glycolate salt. ^{1}H (300 MHz, d_6-DMSO): 3.80 (s, 2), 4.24 (s, 2).

Example (C2): Preparation of (5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methanol



To a 10L reactor was charged HOAc (4.7 L), 2,4-Pentanedione (543 mL, 5.29 mol), and the glycolate salt of (5-amino-1*H*-1,2,4-triazol-3-yl)methanol (944 g, 4.96 mol). The mixture was heated to 100 °C until the solution was homogeneous. After reaching 100 °C, the solution should be nearly homogeneous. The time at 100 °C should be ~15-30 min. After this time, if the solution remains cloudy heating should be discontinued. The resulting solution was cooled to ambient temperature, and MTBE (16 L) was added and the mixture stirred for 30 min. The mixture was filtered through a 14" Buchner, rinsed with MTBE (7 L), and dried in a vacuum oven overnight at 50 °C to provide 518 g (59%) of (5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methanol as a white solid. The filtrate contained significant product, so a second crop was isolated by charging the MTBE filtrates to a 22L reactor and cooling to 0 °C. MTBE (8 L) was added and stirred for 2 hours. The resulting slurry was filtered and dried to yield an additional 173.7 g (20%) of (5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methanol

as a grey solid. Both crops were carried forward. ^{1}H NMR (300 MHz, d_6-DMSO): 2.57 (s, 3), 2.71 (d, 3, J=0.8), 4.83 (uneven d, 2, J=5.7), 5.49 (t, 1, J=5.2), 7.13 (d, 1, J=0.8).

Example (C3): Preparation of 5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde



To a 10 L reactor was sequentially charged CH_2Cl_2 (5.1 L), (5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methanol (900 g, 5.016 mol), and iodobenzene diacetate (1952 g, 4.197 mol). As the iodobenzene diacetate dissolves, there is a significant endotherm (typically down to 15-16 °C). The jacket was set to 23 °C. The mixture was warmed to ambient temperature and Tempo (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical, 49.75 g, 0.28 mol) added in a single charge. The reaction was stirred until 5% of the starting alcohol remained by HPLC. Once the starting material is adjudged to be less than about ~5%, the over-oxidized product begins to be observed. Allowing the reaction to run to further completion leads to an overall diminished yield of the desired product. For this reaction, the desired reaction completion was reached in 2.75 h. MTBE (5.1 L) was then slowly charged to the reactor, causing the product to precipitate, and the slurry stirred for an additional 30 mins. The mixture was filtered, washed twice with 1:1 DCM/MTBE (2 x 1L), and dried in a vacuum oven overnight at 50 °C to provide 500.3 g (74%) of 5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde as an off-white solid. ^{1}H NMR (300 MHz, d_6-DMSO): 2.64 (s, 3), 2.78 (d, 3, J=0.8), 7.38 (d, 1, J=0.9), 10.13 (s, 1).

Example (C4): Preparation of 2-(4-bromo-2-fluorophenyl)-2-methylpropanenitrile

Step A: 2-(4-bromo-2-fluorophenyl)-2-methylpropanenitrile

A 5-L, 3-neck flask was sequentially charged with sodium cyanide (342.19 g, 6.982 moles), Bu_4NBr (49.29 g, 0.1529 mol), water (500 mL) and CH_2Cl_2 (500 mL). After dissolution, the solution was cooled to 10 °C. In a separate vessel, CH_2Cl_2 (320 mL) was added to 4-bromo-2-fluorobenzyl bromide (1626.87 g, 6.080 mol) and the mixture stirred and heated to rt until dissolved. The 4-bromo-2-fluorobenzyl bromide/CH_2Cl_2 solution was charged to an addition funnel, and added slowly to the stirred cyanide solution in order to control the reaction exotherm, maintaining the internal temperature between 25-30 °C. After complete addition, an aliquot was removed and analyzed by HPLC, showing a 2.2:1 ratio of product to starting material. The bath temperature was adjusted to rt and the reaction stirred an additional 19 h. HPLC analysis showed no detectable starting material. The solution was added to a separatory funnel and the lower aqueous layer removed. To the organic phase

was added an aqueous solution of 1% $NaHCO_3$ (8 g $NaHCO_3$ in 800 mL water) and isopropyl ether (IPE, 1600 mL) and the phases mixed well. The aqueous phase is now the top layer. The layers were separated and the lower organic phase added back to the separatory funnel and extracted again with an aq. 1% $NaHCO_3$ solution (800 mL). The phases were separated and the organic layer was added to a 5-L, 3-neck flask set up for distillation. The solution was distilled at atmospheric pressure down to an internal volume of ~1.6 L. To the solution was added IPE (800 mL) and the distillation continued until the internal volume was ~1.6 L. Additional IPE (500 mL) was added and the solution distilled down to an internal volume of 1.6 L. After the solvent displacement was complete, the solution was allowed to cool to 29 °C over 2 hours, and then seeded with crystalline 2-(4-bromo-2-fluorophenyl)-2-methylpropanenitrile causing an exotherm to 36 °C. The solution was allowed to cool with vigorous stirring overnight. The slurry was then cooled in an ice/water bath to an internal temperature <10 °C for 1.5 h. The cold slurry was filtered and the solids rinsed with cold isopropyl ether (2 x 250 mL, <5 °C). The solids were dried under vacuum (no heating, solid melts <40 °C) to provide 1104.80 g (85%) of product as an off-white crystalline solid with purity of 99.8% by HPLC. ^1H NMR of (300 MHz, $CDCl_3$): 3.64 (s, 2), 7.27-7.42 (m, 3).

Step B:

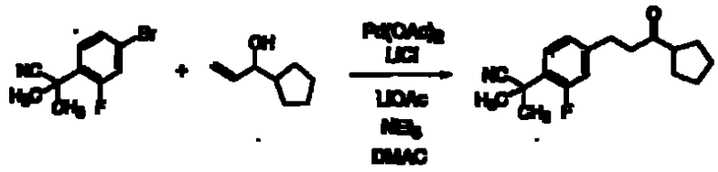


A 2-L, 3-neck flask was charged with (4-bromo-2-fluorophenyl)acetonitrile (100.91 g, 0.4715 mol), MeOTs (158 mL g, 1.034 mol), DMF (400 mL) and THF (400 mL). The headspace was purged with nitrogen and the solution was cooled to –10 °C. The NaOtBu (96.56 g, 1.005 mol) was divided into 4 equal portions that were added separately to the reaction to control the exotherm. Five minutes after the fourth and final charge an aliquot was removed and analyzed by HPLC, verifying reaction completion. The cold bath was removed, and the reaction allowed to stir without cooling (internal temp = 4 °C). The flask was then charged with DABCO (13.02 g, 0.116 mol) to consume the remaining MeOTs. After 30 min an aliquot was removed and analyzed by HPLC, showing no detectable MeOTs. The flask was charged with H_2O (400 mL) and hexanes (400 mL) and the mixture added to a separatory funnel. The phases were mixed well and then separated. The aqueous phase was re-charged to the separatory funnel and re-extracted with hexanes (200 mL). The organic phases from the first two extractions were combined and transferred back to the separatory funnel and washed twice with H_2O (200 mL). The phases were separated and the organic layer was added to a 2-L, 3-neck flask set up for distillation. The solution was distilled under

vacuum (400 torr with an internal temperature of about 50 °C) until no significant solvent distillation occurred. An aliquot of the solution was removed and analyzed by ^{1}H NMR to record the amount of solvents present. The solution of product was held overnight and used without further processing in the next step.

For HPLC monitoring, aliquots were withdrawn and dissolved in CH_3CN/H_2O (70:30). HPLC conditions: Kromasil C4 column, 5um, 4.6x150mm, 40 °C column chamber, flow rate= 1.0 mL/min, 70% CH_3CN/30% aqueous (1.0mL 70% $HClO_4$ in 1L H_2O) isocratic. Percentages reported are at 215 nm. Retention times: starting material = 2.7 min, product = 3.3 min, MsOTs = 2.5 mins, mono-alkylated product = 3.1 min. ^{1}H NMR (300MHz, $CDCl_3$): 6.90-7.00 (m, 2), 7.33-7.39 (m, 1)

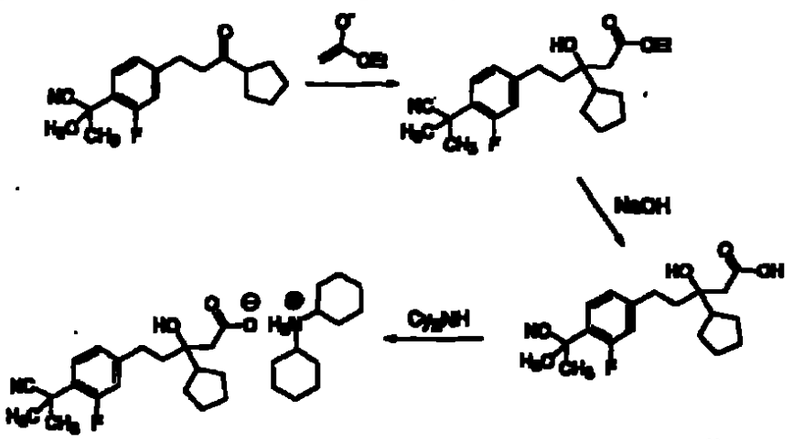
Example (C8): Preparation of 2-[4-(3-cyclopentyl-3-oxopropyl)-2-fluorophenyl]-2-methylpropanenitrile



A nitrogen-purged, 2-L, 3-neck flask containing 2-(4-bromo-2-fluorophenyl)-2-methylpropanenitrile (114.14 g, 0.4715 mol) was sequentially charged (while stirring) with LiCl (39.62 g, 0.9347 mol), LiOAc (15.41 g, 0.2334 mol), DMAc (283 mL), and H_2O (28.3 mL). The solution was then purged (subsurface) with N_2 for 1 h. The flask was then charged with 1-cyclopentyl-prop-2-en-1-ol (73.70 g, 0.5808 mol), Et_3N (8.5 mL, 0.0466 mol, 10% of the total to be added), and $Pd(OAc)_2$ (5.2497 g, 0.0234 mol) followed by a careful purge of the headspace. The reaction was heated towards 75 °C. Once the internal temperature reached 60 °C the reaction may exotherm. It took a total of 20 minutes to heat the reaction to 75 °C. Fifteen minutes after the internal temp had reached 60 °C, an aliquot was removed and analyzed by HPLC, showing a 3:1 ratio of starting material to product. At this point, a second addition of NEt_3 (13.0 mL, 0.0933 mol, 20% of the total to be added) was added to the reaction. Each addition of TEA causes additional exotherms. Twenty minutes after the second NEt_3 addition, an aliquot was removed and analyzed by HPLC, showing a 2:1 ratio of starting material to product. Ten minutes later, the third portion of NEt_3 (46.0 mL, 0.3300 mol, 70% of the total to be added) was added to the reaction. Thirty-five minutes after the final NEt_3 addition, an aliquot was removed and analyzed by HPLC, showing >70:1 ratio of product to starting material. The reaction was heated for 30 min more, then cooled to <30 °C over 15 min. The flask was charged with H_2O (500mL), MTBE (500mL), DARCO (28.5 g), and celite (28.5 g). The solution stirred well for 2 hours then filtered over a cake of celite (28.5 g packed

In a 4" buchner funnel). This filtration of the bilayer through celite was slow, and the vacuum caused a significant portion of the organic solvent to boil away. The cake was washed with MTBE (250mL followed by 125 mL). The filtrate was added to a separatory funnel with an additional portion of MTBE (200 mL), the phases mixed well, and the lower aqueous layer removed. The organic phase was extracted with H_2O (200mL) and the phases mixed well. The lower aqueous layer was removed. The organic layer was extracted with a 5% NaCl/H_2O solution (200mL). The phases were separated and the organic layer was added to a 1L, 3-neck flask. The solution was concentrated by atmospheric distillation until the internal volume was ~2 volumes. After cooling below reflux, an aliquot was removed and analyzed by K-F titration, showing 0.35% H_2O. An additional portion of MTBE (150 mL) was added and distillation continued until the internal volume was again ~2 volumes. After cooling below reflux, an aliquot was removed and analyzed by K-F titration, showing 0.14% H_2O. The solution was cooled under nitrogen and held overnight at rt. The solution was used directly in the next reaction without further processing. ^1H NMR (300MHz, $CDCl_3$): 1.52-1.72 (m, 6), 1.77 (s, 6), 2.73-2.92 (m, 4), 6.90-7.00 (m, 1), 7.33-7.39 (m, 1)

Example (C6): Preparation of 5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid dicyclohexylamine salt

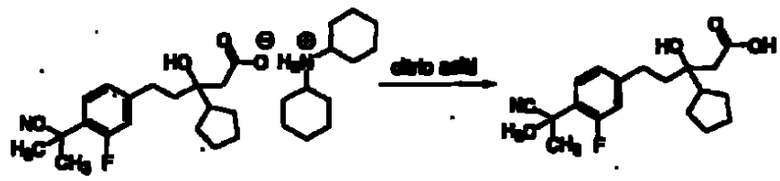


A 3-L, 3-neck flask was charged with LiHMDS (1.0 M in THF, 750mL, 0.75 mol) and purged with nitrogen. This flask was cooled to –64 °C. An addition funnel was then charged with EtOAc (74 mL, 0.7576 mol) and this reagent was slowly added to the reaction vessel. After complete EtOAc addition another addition funnel was charged with a 2-[4-(3-cyclopentyl-3-oxopropyl)-2-fluorophenyl]-2-methylpropanenitrile solution (crude MTBE soln from prior reaction, theor. 135.49 g, 0.4715 mol) and rinsed over with THF (anhydrous, 20 mL). The ketone solution was added to the reaction flask. Five minutes after complete addition a reaction aliquot was removed and analyzed by HPLC, showing 1% 2-[4-(3-cyclopentyl-3-

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cyopropyl)-2-fluorophenyl]-2-methylpropanenitrile. Ten minutes after complete lactone addition, the bath was switched to 0 °C. Once the internal temperature had warmed to -10 °C, 1M NaOH (880 mL) was slowly added. After complete NaOH soln addition, the reaction was heated to 50 °C. After 21 hours an aliquot was removed from the top layer and analyzed by HPLC, showing no detectable ethyl 5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoate. The reaction solution was cooled below 30 °C and added to a separatory funnel with MTBE (1265 mL). The phases were mixed well and separated. An aliquot of the aqueous phase was analyzed by HPLC, verifying no significant product, and this layer was discarded. Water (1265 mL) was added and the phases mixed well and separated. An aliquot of the organic phase was analyzed by HPLC, verifying very little product in this layer, and the organic phase was discarded. The aqueous phase was added to a flask. Concentrated aq. HCl (~40 mL) was added to the aqueous phase until the pH = 2. The mixture was added back to a separatory funnel with IPE (1265 mL) and mixed well. An aliquot of the aqueous phase verified no significant product, and this layer was discarded. The organic layer was dried ($MgSO_4$, 25 g), filtered, and the cake rinsed with IPE (200 mL). The solution was analyzed by K-F titration, showing 0.03% water content. This solution was charged to a 3-L, 3-neck flask. While stirring well, dicyclohexylamine (188 mL, 0.9446 mol) was added. The amine addition caused an exotherm to 28 °C. After 10 min, significant solids were observed. The solution was stirred at rt for 2.5 h. The solution was cooled in a 0 °C bath until the internal temp remains below 5 °C for 2 h. The slurry is filtered, and the solids rinsed with cold (5 °C) IPE (250 mL). The solids were dried to provide 169.88 g of 5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid dicyclohexylamine salt as a white powder. The solids had a 99.4% purity by HPLC and were clean by ^1H NMR.

Example (C7): Preparation of 5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid

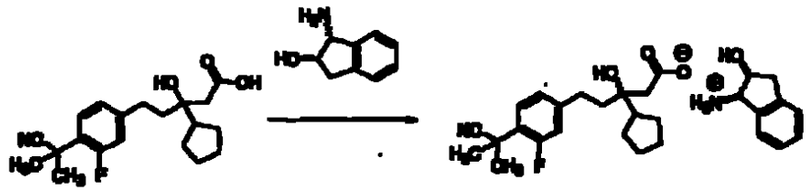


A 3-L, 3-neck flask was charged with 5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid dicyclohexylamine salt (166.0 g, 0.314 moles) and MTBE (1.7 L). The slurry was stirred at 22 °C and 10% aqueous citric acid was added. The mixture was stirred for 45 minutes. The mixture was added to a separatory funnel and the lower aqueous phase was removed. The organic solution was washed with H_2O (50 mL) and

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placed in a 2-L, 3-neck flask. The solution was distilled under atmospheric pressure to ~2.5 volumes, the distillate temperature starting at about 52 °C and stabilizing at ~88 °C. The solution of 5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid (theoretical 0.314 mol) was used directly in the next step.

Example (C8): Preparation of (1R,2S)-(+)-cis-1-amino-2-indanol salt of (3*R*)-5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid



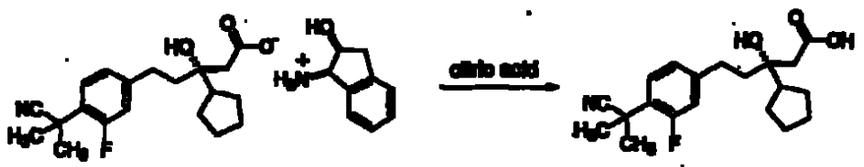
A 2-L, 3-neck flask was charged with (1R,2S)-(+)-cis-1-amino-2-indanol (23.40 g, 0.157 moles) and THF (280 mL). The mixture was stirred and heated to 50 °C, at which point a homogeneous solution was observed. To the heated solution was added a solution of 5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid (108.10 g in MTBE, 0.314 moles, 425 mL total volume) at such a rate that the internal temperature was maintained above 47 °C. After complete addition, MTBE (350 mL) was added at such a rate that the internal temperature was maintained above 47 °C. The stirred mixture was seeded immediately after complete addition of the second portion of MTBE (crystallization progressed rapidly after seeding the mixture). After seeding, heating was discontinued and the mixture was allowed to gradually cool to rt. The mixture was stirred for 17 hours at 21 °C. The mixture was filtered and the solids rinsed with 1:1 MTBE/THF (180 mL). The solids were dried in a vacuum oven (~25 mm-Hg, 50 °C) for 24 h to provide 68.10 g (42 %) of (1R,2S)-(+)-cis-1-amino-2-indanol salt of (3*R*)-5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid as an off-white crystalline solid (yield represents an 85% recovery of the maximum yield of 50% for diastereomerically pure salt). Chiral HPLC analysis of the acid showed the product to be of 99% ee.

Recrystallization of (1R,2S)-(+)-cis-1-amino-2-indanol salt of (3*R*)-5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid: A 3-L, 3-neck flask was charged with (1R,2S)-(+)-cis-1-amino-2-indanol salt of (3*R*)-5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid (65.40 g, 0.132 moles) and IPA (1.7 L). The slurry was stirred and heated to 80 °C until all solids dissolved. At 80 °C, the solution was seeded with (1R,2S)-(+)-cis-1-amino-2-indanol salt of (3*R*)-5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid and heating was discontinued. At 75 °C, the solution was seeded again, at which point substantial crystallization began to occur. The stirred mixture was allowed to cool to rt and granulated for 22 h. The mixture was then filtered

and the solids rinsed with IPA (60 mL). The solids were dried in a vacuum oven (~25 mmHg, 50 °C) for 48 h to provide 60.13 g (92%) of product as a white crystalline solid. Chiral HPLC analysis of the acid showed product with >99% ee.

For determination of e.e.; the solid was dissolved in CH_3CN/H_2O (70/30). HPLC conditions: Chiralcel OJ-RH column, 5 µm, 4.6 x 150 mm, 30 °C column chamber, flow rate = 0.8 mL/min, 55% H_2O (0.1% TFA)/45% CH_3CN (0.1% TFA). Percentages reported are at 205 nm. Retention times: (1R,2S)-(+)-cis-1-amino-2-indanol = 2.2 to 2.4 min; (3*R*)-5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid = 6.4 min; undesired enantiomer = 7.1 min. Chiral HPLC of filtrate indicated a 5:1 mixture of undesired enantiomer to desired enantiomer. ^1H NMR (300 MHz, d_6-DMSO): 1.36-1.62 (m, 6), 1.62-1.74 (m, 2), 1.70 (s, 6), 1.90-2.04 (m, 1), 2.17 (1, d, *J* = 15.3), 2.23 (1, d, *J* = 15.3), 2.56-2.66 (m, 2), 2.89 (dd, 1, *J* = 3.3, 16.2), 3.07 (dd, 1, *J* = 5.8, 16.2), 4.39 (d, 1, *J* = 5.5), 4.52 (dt, 1, *J* = 3.3, 5.6), 7.03-7.47 (m, 7).

Example (C6): Preparation of (3*R*)-5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid



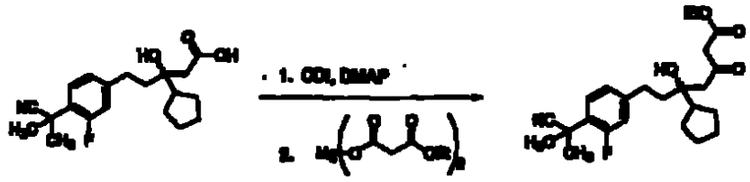
A 2-L, 3-neck flask was charged with (1R,2S)-(+)-cis-1-amino-2-indanol salt of (3*R*)-5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid (59.00 g, 0.119 moles) and MTBE. The mixture was stirred at rt and 10% aqueous citric acid solution was added. After stirring for three hours (if solids are still present, additional mixing time may be required), the mixture was added to a separatory funnel along with an MTBE rinse of the reactor (50 mL) and the lower aqueous layer was removed. The organic phase was washed with H_2O (20 mL). The organic phase containing (3*R*)-5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid was >99% pure by HPLC. The wet organic solution was placed in a 1-L, 3-neck flask and the solution distilled under atmospheric pressure to remove H_2O (pot temp/volume = 765 mL; volume after distillation = 170 mL). The solution was filtered and charged to a 250 mL addition funnel. This solution was used directly in the next step.

HPLC analysis of aqueous and organic phases: aliquots were withdrawn and dissolved in CH_3CN/H_2O (70/30). HPLC conditions: Kromasil C4 column, 5 µm, 4.6 x 150 mm, 40 °C column chamber, flow rate = 1.0 mL/min, 70% CH_3CN/30% aqueous (1.0 mL 70% $HClO_4$ in 1 L

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H_2O) isocratic. Percentages reported are at 215 nm. Retention time: (3*R*)-5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid = 2.7 min.

Example (C10): Preparation of ethyl (5*R*)-7-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-5-cyclopentyl-5-hydroxy-3-oxoheptanoate

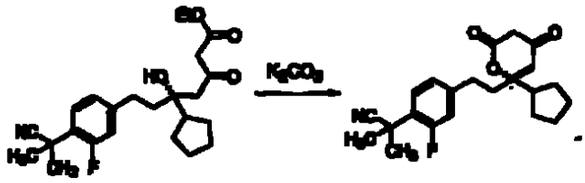


A 1-L, 3-neck flask was charged with CDI (29.00 g, 0.179 moles), DMAP (733 mg, 0.006 moles), and MTBE (70 mL) (notes 1, 2). An MTBE solution of (3*R*)-5-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-3-cyclopentyl-3-hydroxypentanoic acid (41.28 g, 0.119 moles, 170 mL) was added to the stirred mixture over a 30 minute period. The addition funnel was rinsed with THF (5 mL) and the rinse was added to the reaction mixture. The mixture was stirred for 30 min and an aliquot was removed and analyzed by HPLC. Once acyl-imidazole formation was complete, the solution was added to a 500 mL addition funnel. A separate 1-L, 3-neck flask was charged with ethyl magnesium malonate (51.30 g, 0.179 moles) and THF (100 mL) (the solids did not dissolve in THF, even after warming to 40 °C). The stirred mixture was heated to 40 °C and the acyl-imidazole solution was slowly added to the mixture. Stirring was continued at 40 °C, and aliquots were periodically removed and analyzed by HPLC for completion. After the reaction was complete, heating was discontinued and the solution allowed to cool to rt. The solution was diluted with IPE (200 mL) and 1 N HCl (360 mL), the mixture was stirred for 15 minutes, and the phases were separated. The organic phase was extracted with H_2O (10 mL), the phases separated, and the organic layer was added to a 1-L, 3-neck flask. The solution was distilled to a minimum of ~3.3 volumes to remove H_2O (the distillate temperature was 48 °C during azeotrope distillation and the distillation was ended after the distillate temperature was steady at ~60 °C). The solution was used directly in the next step.

For HPLC monitoring of reaction, aliquots were withdrawn and dissolved in CH_3CN/H_2O (70/30). HPLC conditions: Kromasil C4 column, 5 µm, 4.6 x 150 mm, 40 °C column chamber, flow rate = 1.0 mL/min, 70% CH_3CN/30% aqueous (1.0 mL 70% $HClO_4$ in 1 L H_2O) isocratic. Percentages reported are at 215 nm. Retention time: imidazole = 1.4 min, acyl-imidazole = 2.2 min, anhydride byproduct = 2.4 min, ethyl (5*R*)-7-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-5-cyclopentyl-5-hydroxy-3-oxoheptanoate = 2.7 min. ^1H NMR (300 MHz, $CDCl_3$): 1.29 (t, 3, J = 7.2), 1.40-1.55 (m, 3), 1.57-1.72 (m, 6), 1.86 (m, 6), 2.12 (m,

1), 2.65 (*m*, 2), 2.82 (d, 1, *J* = 5.1), 3.66 (*m*, 2), 3.76 (*m*, 3), 4.22 (q, 2, *J* = 7.2), 6.97 (*m*, 2), 7.36 (app. t, 1, *J* = 8.1).

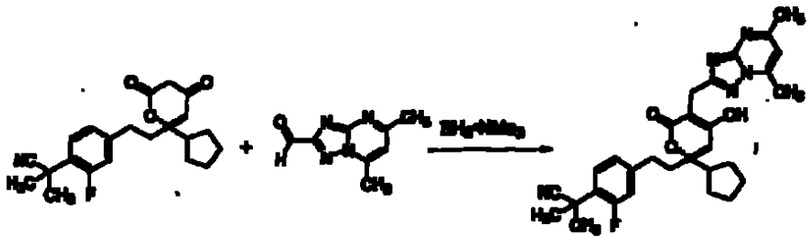
Example (C11): Preparation of 2-(4-[2-[(2*R*)-2-cyclopentyl-4,6-dioxotetrahydro-2*H*-pyran-2-yl]ethyl]-2-fluorophenyl)-2-methylpropanenitrile



A solution of ethyl (5*R*)-7-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-5-cyclopentyl-5-hydroxy-3-oxoheptanoate (49.61 g, 0.1168 mol, 135 mL total volume) in a 1-L, 3-neck flask was charged with MeOH (120 mL) and K_2CO_3 (25.00 g, 0.1809 mol) and the stirred mixture was heated to 50 °C for 4 hours. An aliquot was removed and analyzed by HPLC and showed the reaction to be more than 99% complete. The solution was cooled to rt and charged with IPE (50 mL) and H_2O (200 mL). The mixture was stirred for 5 minutes and placed in a 2 L separatory funnel to separate phases. The reaction vessel was rinsed with H_2O (10 mL) and the rinse was added to the separatory funnel. The phases were separated and the product-containing aqueous phase was extracted with IPE (20 mL). The layers were separated and the aqueous phase added back to the funnel. To the aqueous phase was added 2-Me-THF (300 mL), MTBE (100 mL), and 1M HCl (~360 mL) until the pH of the aqueous phase was ~4.75. The phases were mixed well and the aqueous phase was removed. The organic phase was washed with H_2O (20 mL) and then placed in a 500-mL, 3-neck flask. The solution was concentrated by atmospheric distillation to ~3.3 vol. (the distillate temperature during azeotrope started at 38 °C, then raised to 48 °C, and finally stabilized at 57 °C). The solution was cooled to 25 °C and an aliquot was analyzed by Karl-Fischer titration. The solution was then reheated to 55 °C and heptane (50 mL) was added at such a rate that the internal temperature was kept above 53 °C (the addition of heptane when the internal temperature was less than 50 °C resulted in oiling). The solution was then seeded with solid 2-(4-[2-[(2*R*)-2-cyclopentyl-4,6-dioxotetrahydro-2*H*-pyran-2-yl]ethyl]-2-fluorophenyl)-2-methylpropanenitrile, followed by the addition of heptane (250 mL). The stirred mixture was allowed to gradually cool to rt. After stirring for 15 min at rt, the mixture was filtered and the solids rinsed with 1:1 IPE/heptane (75 mL). The solids were dried to provide 30.92 g (70%) of 2-(4-[2-[(2*R*)-2-cyclopentyl-4,6-dioxotetrahydro-2*H*-pyran-2-yl]ethyl]-2-fluorophenyl)-2-methylpropanenitrile as granular crystals. The solids were dried in a vacuum oven (~25 mmHg, 50 °C) for 20 h and were determined to be >99% pure by HPLC analysis.

HPLC conditions: aliquots were withdrawn and dissolved in CH_3CN/H_2O (80/20). HPLC conditions: Kromasil C4 column, 5 µm, 4.6 x 150 mm, 40 °C column chamber, flow rate = 1.0 mL/min, 80% CH_3CN/20% aqueous (1.0 mL 70% $HClO_4$ in 1 L H_2O) isocratic. Percentages reported are at 215 nm. Retention time: 2-(4-[2-[(2*R*)-2-cyclopentyl-4,6-dioxotetrahydro-2*H*-pyran-2-yl]ethyl]-2-fluorophenyl)-2-methylpropanenitrile = 2.2 min, ethyl (5*R*)-7-[4-(1-cyano-1-methylethyl)-3-fluorophenyl]-5-cyclopentyl-5-hydroxy-3-oxoheptanoate = 2.7 min, by-product 1 = 2.5 min, by-product 2 = 2.9 min, by-product 3 = 3.1 min. ^1H NMR (300 MHz, $CDCl_3$): 1.46-1.73 (m, 7), 1.77 (s, 7), 1.91 (m, 2), 2.27 (m, 1), 2.66 (t, 2, *J* = 7.5), 2.77 (s, 2), 3.43 (d, 2, *J* = 1.4), 6.92 (m, 2), 7.39 (app. t, 1, *J* = 8.2).

Example (C12): Preparation of 2-[4-[2-[(2*R*)-2-cyclopentyl-6-[(5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]ethyl]-2-fluorophenyl]-2-methylpropanenitrile



A 1-L, 3-neck flask was sequentially charged with 2-(4-[2-[(2*R*)-2-cyclopentyl-4,6-dioxotetrahydro-2*H*-pyran-2-yl]ethyl]-2-fluorophenyl)-2-methylpropanenitrile (30.01 g, 0.0808 moles), and IPA (150 mL). After purging with N_2, the flask was charged with BH_3-NMe_3 (8.27 g, 0.113 moles) and 5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidine-2-carbaldehyde (21.37 g, 0.121 moles). After 15 min an aliquot was removed and analyzed by HPLC (typically, the starting material is in the 5-6% range before quench). The flask was charged with isopropyl acetate (IPAc, 150 mL) and 1M HCl (150 mL). After 30 min an aliquot was removed and analyzed by HPLC to verify the decomplexation of boron. The reaction was transferred to a separatory funnel and the aqueous phase was removed. The organic phase was extracted with H_2O (150 mL) and the lower aqueous layer was removed. The organic layer was added to a 500 mL, 3-neck flask set up for distillation. The solution was distilled to a minimum level of 5 vols., IPAc (100 mL) was added, and the distillation was continued. This process was repeated until IPA was removed from the solution and the distillation was continued to achieve 5 vol. (the distillation was judged to be complete when the distillation head maintained a steady temperature of about 86-89 °C). The solution was slowly cooled to room temperature and stirred overnight. The mixture was filtered and the solids were washed with IPAc (2 x 25 mL). The solids were transferred to a 1-L, 3-neck flask with IPAc (150 mL) and IPA (150 mL) and heated to 50 °C. The solution was cooled to an internal temperature of 30 °C and filtered

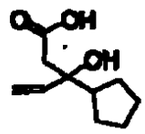
through a 0.45 µm membrane filter. The flask was rinsed with an IPAc/IPA mixture (1:1, 100 mL). The filtrate was placed in a 500 mL, 3-neck flask set up for distillation. The solution was distilled to a minimum level of 5 vol. then IPAc (100 mL) was charged and the distillation was continued. The process was repeated until IPA was removed from the solution and the distillation was continued to achieve 5 vol. (the distillation was judged to be complete when the distillation head maintained a steady temperature of about 86-89 °C). The solution was slowly cooled to rt and stirred overnight. The mixture was filtered and the solids were washed with IPAc (2 x 25 mL) and dried in a vacuum oven (25 mmHg, 50 °C) overnight. The dry solids were charged to a flask with H_2O (500 mL HPLC grade), heated to 75 °C, and stirred vigorously for 18 h. The slurry was cooled, filtered over polycloth, and the solids washed with H_2O (2 x 100 mL) and dried in a vacuum oven (25 mmHg, 50 °C) overnight to provide 23.66 g (55%) of 2-[4-(2-[(2*R*)-2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile as a white crystalline solid.

For HPLC monitoring, aliquots were withdrawn and dissolved in CH_3CN/H_2O (70:30). HPLC conditions: Kromasil C4 column, 5µm, 4.6x150mm, 40 °C column chamber, flow rate= 1.0 mL/min, 70% CH_3CN/30% aqueous (1.0mL 70% $HClO_4$ in 1L H_2O) isocratic. Percentages reported are at 215 nm. Retention times: 2-(4-[2-[(2*R*)-2-cyclopentyl-4,6-dioxotetrahydro-2*H*-pyran-2-yl]ethyl]-2-fluorophenyl)-2-methylpropanenitrile = 2.67 min, 5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde = 1.5 min, 2-[4-(2-[(2*R*)-2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile = 2.3 min, Boron/pd. complex = 2.8 min

The product contained no detectable enantiomer by chiral HPLC analysis. For determination of *e.a.*, the solid was dissolved in CH_3CN/H_2O (70/30). HPLC conditions: Chiralcel OJ-RH column, 5 µm, 4.6 x 150 mm, 30 °C column chamber, flow rate = 0.8 mL/min, 55% H_2O (0.1% TFA)/45% CH_3CN (0.1% TFA). Percentages reported are at 205 nm. Retention times: undesired enantiomer = 6.3 min, 2-[4-(2-[(2*R*)-2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]ethyl)-2-fluorophenyl]-2-methylpropanenitrile = 7.3 min. ^1H NMR (300MHz, $CDCl_3$): 1.22-1.85 (m, 9), 1.80 (s, 6), 1.99-2.06 (m, 2), 2.33-2.48 (m, 1), 2.58 (d, 1, *J* = 17.7), 2.68-2.76 (m, 2), 2.71 (s, 3), 2.82 (d, 1, *J* = 17.7), 2.83 (s, 3), 4.14 (br s, 2), 6.87-6.98 (m, 3), 7.37 (app t, 1, *J* = 8.2).

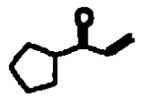
Example C(13): 3-Cyclopentyl-3-hydroxypent-4-enoic acid

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Ethyl 3-cyclopentyl-3-hydroxypent-4-enoate (22.12 g, 104.34 mmol), from step 2 below, was dissolved in MeOH (100 mL) and solution of NaOH (8.35 g) in H_2O (100 mL) was added. The reaction was stirred overnight at room temperature. The reaction mixture was partitioned between H_2O and IPE. The aqueous layer was made acidic with 4N HCl and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give and off white solid that was recrystallized from hot hexanes. (18g, 94% yield). ^1H NMR (300MHz, $CDCl_3$): δ 1.26-1.89 (m, 8H), 1.99-2.08 (m, 1H), 2.60 (d, J = 15.6, 1H), 2.68 (d, J = 15.6, 1H), 5.17-5.33 (m, 2H), 5.82-5.92 (m, 1H). ESIMS (M+H-): 183.

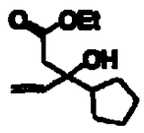
Step 1: 1-Cyclopentyl-propenone



Cyclopentane carboxylic acid (15 mL, 138.41 mmol) was dissolved in CH_2Cl_2 (185 mL) and DMF (0.25 mL). The reaction was cooled to 0 °C and oxalyl chloride (13.9 mL, 159.19 mmol) was slowly added. After stirring for 1 hour at room temperature, it was cooled again to 0 °C and a solution of $AlCl_3$ (20.30 g, 152.28 mmol) and vinyltrimethylsilane (21.38 mL, 138.44 mmol) in CH_2Cl_2 (180 mL) was added slowly via addition funnel. The reaction mixture was stirred for 10 minutes and then poured over ice. Concentrated HCl was added until the precipitate of $Al(OH)_3$ dissolved and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to a yellow oil that was used without further purification.

The oil was dissolved in CH_3CN (100 mL), treated with triethyl amine (24 mL), and stirred at 5 °C for 1 hour. The reaction mixture was poured into 5% $KHSO_4$ (100 mL) and extracted with ethyl acetate (3x100 mL). The organic layers were washed with brine, dried over Na_2SO_4 and carefully concentrated (volatile) to give a yellow oil that was used crude without further purification. (15.7 g, 94% yield). ESIMS (M+H-): 125.

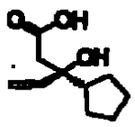
Step 2: Ethyl 3-cyclopentyl-3-hydroxypent-4-enoate



A magnetically stirring solution of lithium hexamethyldisilazine 1 M in THF (253.23 mL) was cooled to -78 °C. Ethyl acetate (24.74 mL, 253.23 mmol) was slowly added and

reaction stirred for 20 min at this temperature. 1-Cyclopentyl-propanone, from step 1 above, was dissolved in THF (40 mL) and added to lithium anion via canula over a period of 30 minutes. The reaction was stirred at -78 °C for 1 hour. The reaction mixture was partitioned between 1N HCl and IPE. The layers of the resulting reaction mixture were separated and the organic layer was washed with brine (1 x 10 mL), then dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (20% EtOAc in Hexanes) to give the desired product as a yellow oil (22.12 g, 91%). ^1H NMR (400MHz, $CDCl_3$): δ 1.25 (t, J = 7.2, 3H), 1.35-1.68 (m, 8H), 1.96-2.03 (m, 1H), 2.53 (d, J = 15.2, 1H), 2.60 (d, J = 15.2, 1H), 4.13 (q, J = 7.2, 2H), 5.11-5.32 (m, 2H), 5.80-5.90 (m, 1H). ESIMS (MH+): 213.

Example C(14): (3R)-3-cyclopentyl-3-hydroxypent-4-enoic acid (ENANTIOMER 1)

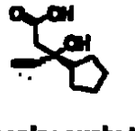


To a solution of 3-cyclopentyl-3-hydroxypent-4-enoic acid (1 g, 5.43 mmol) in EtOAc (27 mL) from example C(13) under stirring was added a solution of (S)-1,2,3,4-tetrahydro-1-naphtylamine* (0.399 g, 2.71 mmol) in EtOAc (13 mmol). After 10 minutes a white precipitate formed. This precipitate was collected on paper and recrystallized from hot EtOAc. The precipitate was partitioned between EtOAc (5 mL) and 1N HCl (5 mL) and the organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo to an oil which solidified upon standing (0.43 g, 43%).

^1H NMR (300MHz, $CDCl_3$): δ 1.26-1.69 (m, 8H), 1.99-2.08 (m, 1H), 2.60 (d, J = 15.6, 1H), 2.68 (d, J = 15.6, 1H), 5.17-5.33 (m, 2H), 5.82-5.92 (m, 1H). ESIMS (M+-): 183. 98% ee, Retention time 25.02 min (Chiralpack OD-RH, 150 x 4.6 mm,0.6 mL/min, 15% B and 85% buffer for 30 min).

*Other amines suitable for the resolution are: (S)-(-)-1-(2-naphthyl)ethylamine and (R)-(-)-1-(2-naphthyl)ethylamine and (1R,2S)-(-)-norephedrine and (1S,2R)-(+)-norephedrine.

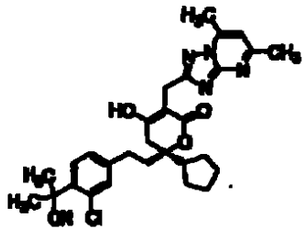
Example C(15): (3S)-3-cyclopentyl-3-hydroxypent-4-enoic acid (ENANTIOMER 2)



The title compound is prepared analogously to example C(14) (enantiomer 1) above where (R)-1,2,3,4-tetrahydro-1-naphtylamine* is substituted in place of (S)-1,2,3,4-tetrahydro-1-naphtylamine of that example. *Other amines amines suitable for the resolution are: (S)-(-)-

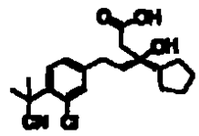
1-(2-naphthyl)ethylamine and (R)-(-)-1-(2-naphthyl)ethylamine and (1R,2S)-(-)-norephedrine and (1S,2R)-(+)-norephedrine.

Example C(16): 2-[2-chloro-4-(2-[(2S)-2-cyclopentyl-5-[[5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)phenyl]-2-methylpropanenitrile.



The title compound was prepared analogously to example A(1) where 2-[2-chloro-4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-phenyl]-2-methyl-propionitrile, from step 2 below was substituted in place of 6-cyclopentyl-6-[2-(5-ethyl-4-hydroxy-2-propoxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione in that example. ^{1}H NMR (400MHz, DMSO-d_6): δ 1.39-1.84 (m, 8H), 1.67 (s, 6H), 2.01-2.05 (m, 2H), 2.36-2.46 (m, 7H), 2.51-2.57 (m, 2H), 2.69(d, *J* = 17 Hz, 2H), 3.61(d, *J* = 16 Hz, 1H), 3.72 (d, *J* = 16 Hz, 1H), 6.94 (s, 1H), 7.25 (s, 1H), 7.28 (s, 1H), 7.35 (d, *J* = 8 Hz, 1H), 10.75 (s, 1H). IR (neat): 2243, 2355 (CN), 1668, 1625, 1543, 1380. MS(ESI): 549 $(M+H)^+$. Positive rotation. HPLC (Chiralpak AS-H, 140 Bar, 2.5 mL/min, 35% MeOH. (12 min retention time).

Step 1: 5-[3-Chloro-4-(cyano-dimethyl-methyl)-phenyl]-3-cyclopentyl-3-hydroxy-pent-4-enoic acid

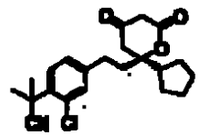


A mixture of 2-(4-bromo-2-chloro-phenyl)-2-methyl-propionitrile (0.61g, 2.34 mmol), from step 4 of example B(22) , (3*R*)-3-cyclopentyl-3-hydroxypent-4-enoic acid (0.43 g, 2.34 mmol, example C(14) , $Pd(OAc)_2$ (0.01 g, 5 mol%) and NaOAc (0.24 g, 2.93 mmol). In DMAC (5 mL) was heated at 90 °C overnight. The reaction mixture was cooled to room temperature and partitioned between 1N HCl and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dark brown oil. Flash column chromatography (0% to 40% EtOAc in hexanes) gave a light brown oil. The oil was dissolved in EtOH (10 mL) and treated with $Pd(OH)_2$ (0.23 g) The mixture was stirred under a balloon of hydrogen for 1 hour. The reaction mixture was filtered through a pad of celite washing with EtOAc. The filtrate was concentrated to an orange oil and purified by flash column chromatography to give the product as a yellow solid (0.47g, 100%). ^{1}H NMR (300 MHz, CDCl3): δ 1.4-1.72 (m, 10 H), 1.85 (s,

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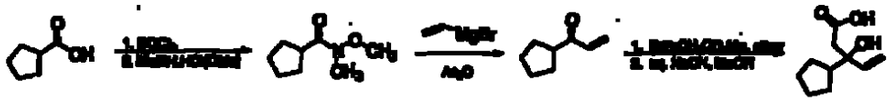
f), 2.11-2.18 (m, 1 H), 2.56-2.73 (m, 4 H), 7.10 (d, J = 7.9 Hz, 1 H), 7.26 (s, 1H), 7.36 (d, J = 7.9 Hz, 1 H). ESMS (MNa+): 364.

Step 2: 2-[3-Chloro-4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-phenyl]-2-methyl-propionitrile.

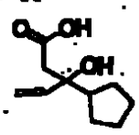


5-[3-Chloro-4-(cyano-dimethyl-methyl)-phenyl]-3-cyclopentyl-3-hydroxy-pent-4-enoic acid, from step 1 above, was dissolved in methyl tert-butyl ethylmalonate (3 mL). 4-DMAP (0.16 g, 0.13 mmol) and CDI (0.27 g, 1.66 mmol) were added and the reaction mixture was stirred under argon for 2 hours. In a separate flask was placed magnesium-bis-monoethyl malonate (0.74 g, 2.58 mmol) was suspended in THF (3 mL) and the mixture was heated to 42 °C. The acylimidazole solution was added via cannula to the malonate mixture and the reaction was heated to 42 °C for 2 hours. The solvent was removed in vacuo to give a residue that was partitioned between 1 N HCl and EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to a clear oil (0.56 g, 100%).

The oil was dissolved in a 0.3 M NaOH solution in MeOH/H_2O 1:1 (6 mL), and stirred overnight at room temperature. The reaction mixture was partitioned between H_2O and IPE. The aqueous layer was made acidic with 1N HCl and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give the product (0.45g, 90% yield). ^1H NMR (400MHz, $CDCl_3$): δ 1.39-1.71 (m, 8H), 1.81-1.87 (m, 8H), 2.10-2.15 (m, 1H), 2.59-2.68 (m, 2H), 3.51 (s, 2H), 3.75 (s, 2H), 7.11 (dd, J = 8.1 Hz, 1.8), 7.27 (d, J = 1.8 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H). ESMS (MH+): 388.



Example C(17): 3-Cyclopentyl-3-hydroxypent-4-enoic acid

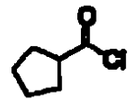


A solution of NaOH (30 g in 300 ml water, 0.75 mol) was added into a mixture of *methyl 3-cyclopentyl-3-hydroxypent-4-enoate (74 g, 0.37 mol, from step 4 below)* in methanol (300 ml) at 15 °C. After addition, the mixture was stirred at room temperature overnight. Methanol was removed in vacuo and the aqueous solution was extracted with Et_2O (200 mL x 2) and ethyl acetate (200 mL x 2) to remove neutral impurities. The aqueous phase was

acidified to pH=2 with 4N of HCl and extracted with CH_2Cl_2 (200 mL x 2 + 100 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4. After evaporation, the obtained crude compound was re-crystallized from hexane (about 100 ml) to afford 44.3 g of pure product and 7 g of crude material was recovered.

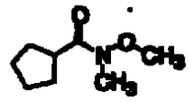
^1H NMR (300MHz, $CDCl_3$): δ 1.26-1.69 (m, 8H), 1.89-2.08 (m, 1H), 2.60 (d, J = 15.8, 1H), 2.69 (d, J = 15.8, 1H), 5.17-5.33 (m, 2H), 5.82-5.92 (m, 1H). ESMS (MH-): 183.

Step 1: Cyclopentanecarbonyl chloride



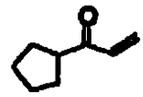
Cyclopentane carboxylic acid (100 g) was dissolved in 250mL of $SOCl_2$ and heated to reflux for about 3h. The excess $SOCl_2$ was removed under reduced pressure. The acid chloride was obtained via distillation in high vacuum (102 g).

Step 2: *N*-methoxy-*N*-methylcyclopentanecarboxamide



Cyclopentane carbonyl chloride (65 g, 0.49 mol) was added dropwise into a mixture of Et_3N (180 mL, 1.3 mol) and N,O-dimethyl hydroxylamine hydrochloride (50 g, 0.52 mol) in anhydrous CH_2Cl_2 at 0 °C. After the addition, the reaction mixture was allowed to stir at ambient temperature overnight. To the reaction mixture was added about 100 g of crushed ice followed 100 g of water. The mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL x 2). The combined organic layers were washed with 1N HCl, water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford 61 g of desired product as oil in 78.8% of yield.

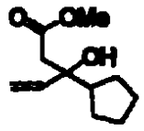
Step 3: 1-Cyclopentyl-propenone



To a solution of (Methoxy-*N*-methylcyclopentanecarboxamide (40 g, 0.25 mol) in 200 mL of anhydrous THF was added dropwise a solution of vinylmagnesium bromide (1.0 M solution in THF, 300 mL, 0.3 mol) at -30 °C under nitrogen. The reaction mixture was then stirred at room temperature overnight. The reaction was quenched by addition of acetic anhydride (48 mL) followed by methanol (48 mL). The solution was concentrated under reduced pressure, and 300 mL of ether was added followed by 300mL of 1N HCl. The mixture was separated, and the aqueous layer was extracted with ether (100 mL x 2). The organic

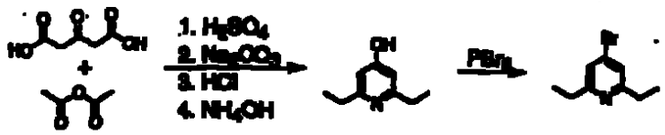
layers were combined, washed with water, brine and dried over Na_2SO_4. After evaporation, 31 g of crude compound were obtained and used in the next step without further purification.

Step 4: Methyl 3-cyclopentyl-3-hydroxypent-4-enoate

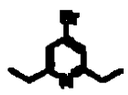


To a suspension of activated zinc (27 g, 0.4 mol) in anhydrous ethyl ether (200 mL) was added dropwise a solution of methyl bromoacetate (24 ml, 0.24 mol) and 1-cyclopentyl-propenone (31 g, 0.24 mol) in 100 mL anhydrous ethyl ether. Once the reaction had commenced, the remainder of the solution was added at such a rate as allowing a gentle refluxing. When the addition was complete, the mixture was heated under reflux for another 3h. The mixture was cooled and quenched with 10% of aq. AcOH. Excess zinc was removed by filtration. The filtrate was treated with saturated ammonium chloride. The ether layer was separated and the aqueous phase was extracted with ether (100 ml x 2). The combined extracts were washed with water, brine, dried over Na_2SO_4 and concentrated to give the product (36.4 g).

Example (C18): 4-bromo-2,6-diethyl-pyridine

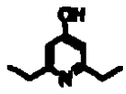


4-Bromo-2,6-diethyl-pyridine



2,6-Diethyl-pyridin-4-ol from step 1 below (4 g, 26.45 mol) was dissolved in $CHCl_3$ (40 mL) and PBr_3 (11.43 g, 26.45 mmol). The reaction was heated at 60 °C for 1 hours and the $CHCl_3$ was evaporated. The residue was heated at 120 °C for 6 hours. After cooling, the reaction mixture was carefully added to a solution made with water (500 mL) and NaOH pellets (45 g) then extracted 3 x EtOAc (100 mL). The combined organic layers were dried over sodium sulfate and concentrated to a brown oil which was purified via short plug of silica gel with 10% EtOAc/Hexanes (x 1000 mL).

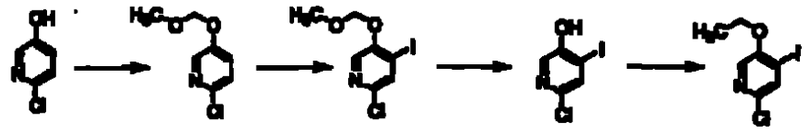
Step 1: 2,6-Diethyl-pyridin-4-ol



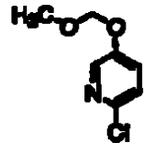
Acetonedicarboxylic acid (Aldrich, 165115) (60 g, 0.41 mol) was added rapidly to propionic anhydride (Aldrich, 240311) (170 mL, 1.3 mol) containing concentrated sulfuric acid (2 mL), and the reaction mixture was heated at 100 °C for 30 minutes with stirring. The solution was cooled rapidly in an ice-salt mixture, and just when a white solid mass was forming, the reaction was added to cold water (500 mL), stirred and filtered immediately. The product was air-dried and placed in a 3 L flask and treated with aqueous 10% sodium carbonate (600 mL). The resulting paste was stirred with a stirrer and heated at 100 °C for 30 min. Carbon dioxide evolved and a light yellow solution was obtained which was heated at 95-90 °C for further 60 min. The solution was cooled and acidified with aqueous 30% acetic acid until no more carbon dioxide was evolved. The white precipitate was filtered, washed with water, air-dried and then added to concentrate hydrochloric acid (120 mL) in a 2 L round-bottomed flask, and the mixture was heated under reflux for 4 hours. The solution was cooled in ice and neutralized by adding it to a stirred solution of sodium carbonate (about 115 g) in water (about 800 mL). The neutral solution was extracted thoroughly with EtOAc. The extract was dried and stripped of solvent to give product 2,6-Diethyl-4-pyrone as a brown oil. (Yates et al, JOC, vol. 34, No, 12, 1969, p4046-4052)

The above product was dissolved in 28% NH_3 in H_2O (10 equivalents) and the reaction was heated at 50 °C overnight. The next morning, the solvents were completely removed to yield the title compound as a brown oil, which was submitted crude to the bromination reaction.

Example (C19): 2-chloro-5-ethoxy-4-iodo-pyridine



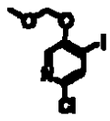
Step1: 2-Chloro-5-methoxymethoxy-pyridine



Sodium hydride (60 % dispersion in oil, 1.83 g, 46.0 mmol) was suspended in anhydrous DMF (50 mL) at under N_2 at room temperature with stirring. A solution of 2-chloro-5-hydroxy-pyridine (5.0 g, 38.2 mmol) in anhydrous DMF (20 mL) was added dropwise over 30 min. Stirring at room temperature was continued for 1.5 hours. Chloromethyl methylether (3.92 mL, 44.1 mmol) was next added neat over 20 min. Stirring was continued at room temperature for 12 hours. The mixture was partitioned between water and EtOAc. The

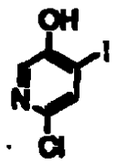
organics were washed with brine, dried over Na2SO4, filtered and concentrated. The crude residue was chromatographed on silica gel, eluting with 20% EtOAc in Hexanes to provide the desired product as a clear oil (6.4 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.36 (d, *J* = 8.6 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 5.19 (s, 2H), 3.50 (s, 3H).

Step 2: 2-Chloro-4-iodo-5-methoxymethoxy-pyridine



2-Chloro-5-methoxymethyl-pyridine (1 g, 5.8 mmol) was dissolved in anhydrous THF (30 mL) and cooled to –78 °C with magnetic stirring under N_2. Next, t-BuLi (1.7M in pentane (5.76 mL, 11.5 mmol) was added over 10 min. The resulting brown solution was allowed to stir at –78 °C for 20 min. Iodine (2.19 g, 8.6 mmol) was added as a solution in THF (15 mL) dropwise over 20 min. The mixture was stirred at –78 °C for 1 hour. The reaction was quenched at –78 °C with water and allowed to warm to room temperature. The mixture was partitioned between EtOAc and water. The aqueous was extracted with EtOAc (2 x 100 mL). The combined organics were washed with saturated aqueous sodium thiosulfate (2 x 100 mL) and brine (100 mL). The organics were dried over Na2SO4, filtered, and concentrated. The yellow/orange residue was triturated with hexanes to provide a yellow solid (0.88 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.75 (s, 1H), 5.25 (s, 2H), 3.50 (s, 3H).

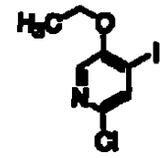
Step 3: 6-Chloro-4-iodo-pyridin-3-ol



2-Chloro-4-iodo-5-methoxymethoxy-pyridine (0.8 g, 2.7 mmol) was dissolved in THF (4 mL) and 3N HCl (6 mL). The mixture was heated to 60 °C with magnetic stirring. Heating was maintained for 3 hours. The mixture was cooled to room temperature and the pH was adjusted to 7 with the slow addition of saturated aqueous sodium bicarbonate. The result was extracted with EtOAc (3 x 50 mL), dried over Na_2SO_4, filtered and concentrated. The solid was suspended in EtOAc and stirred for 12 hours at room temperature. The mixture was filtered and the filtrate was concentrated to yield an off white solid (0.63 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6): δ11.10 (br s, 1H), 7.89 (s, 2H).

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Step 4: 2-Chloro-5-ethoxy-4-iodo-pyridine



6-Chloro-4-iodo-pyridin-3-ol (0.41 g, 1.62 mmol) was dissolved in anhydrous DMF (4 mL) and stirred at room temperature. Potassium carbonate (0.67 g, 4.9 mmol) and iodoethane (0.40 mL, 4.9 mmol) were added sequentially. The mixture was heated to 60 °C and maintained for 2 hours. The mixture was cooled to room temperature and filtered. The filtrate was diluted with diethyl ether (25 mL) and washed with 20% aqueous citric acid (25 mL). The aqueous was extracted with diethyl ether (2 x 20 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was triturated with hexane resulting in a tan solid (0.42 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ7.80 (s, 1H), 7.74 (s, 1H) 4.18 (q, *J* = 7.1 Hz, 2H), 1.51 (t, *J* = 7.1 Hz, 3H).

Example D1: Antiviral Activity

The compounds described herein were tested for activity with HCV polymerase. Recombinant HCV polymerase was tested for its ability to perform primer/template-directed transcription in assays that contained 30 mM tris-HCl pH 7.2, 10 mM $MgCl_2$, 20 mM NaCl, 1mM Dithiothreitol (DTT), 0.05% Tween-20, 1% glycerol, 5 pmoles biotin-dG_{12} (primer), 0.5 pmoles poly$(rC)_{200}$ (template), 1 μM GTP, 0.1-0.3 uCi α-^{33}P-GTP, and 2.5 pmoles (0.15 μg) HCV polymerase protein in a final volume of 75 μL. Reactions were initiated by addition of enzyme and incubated 30 minutes at 30°C. Reactions were stopped by addition of 33 mM EDTA, and polynucleotide products were collected by filtration through Diethylaminoethyl (DE) Filtermat papers (Wallac). Unincorporated triphosphate was removed by washing the filters with 8% dibasic sodium phosphate. The filters were counted in a Packard Tri-Lux Microbeta scintillation counter (Packard Bioscience, Meriden, CT). Compounds to be tested were added at various concentrations, e.g., 1μm to 50 μm, from stocks in 10% DMSO-water (final DMSO is 1% in reaction).

IC_{50} values were estimated from the primary cpm data (collected in triplicate) using the formula: cpm (I)= cpm (no inhibitor)(1- ([I]/([I] + IC_{50}))). An IC_{50} value represents the concentration (in μM) of a compound that provides 50% inhibition of polymerase-directed transcription in the above assay. A percent inhibition value is expressed for a compound where it was impractical to calculate an IC_{50} value with available data. If the IC_{50} estimated by the above equation was less than 200 nM, it was recalculated using the following equation, which takes into account the enzyme concentration (30 nM) in the assay: cpm(I) = cpm(no

Inhibitor)(1-((((I+IC_{50}+30e-9)-sqrt(((I+IC_{50}+30e-9)^2)-4 x 30e-9 x I)))/((2) (30e-9))). Curve fitting was performed using the program KaleidaGraph (Synergy Software, Reading, Pennsylvania).

Inhibition concentration (IC_{50}) data as determined for exemplary compounds of the invention are presented in Table 1 below.

TABLE 1

Example No.	IC50 (μM)
A(1)	0.003
A(101)	0.008
A(111)	0.005
A(116)	0.005
A(117)	0.005
A(12)	0.002
A(21)	0.001
A(22)	0.004
A(23)	0.008
A(13)	0.001
A(24)	0.014
A(26)	0.004
A(30)	0.004
A(31_	0.006
A(37)	0.003
A(47)	0.005
A(48)	0.007
A(50)	0.004
A(57)	0.003
A(58)	0.001
A(59)	0.003
A(74)	0.003
A(75)	0.005
A(76)	0.005
A(77)	0.005
A(78)	0.012
A(84)	0.072
A(85)	0.083
A(86)	0.086
A(89)	0.009
A(94)	0.027
A(95)	0.04
A(96)	0.008
A(97)	0.011
B(14)	0.026
B(18)	0.17
B(19)	1.1
B(20)	0.005
B(22)	0.042

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B(23)	0.14
B(24)	0.1
B(25)	0.033
B(26)	0.005
A(29)	0.002
A(79)	0.012
A(103)	0.003
A(104)	0.006
A(106)	0.004
A(107)	0.006
A(108)	0.006
A(109)	0.006
A(114)	0.005
A(115)	0.006
A(118)	0.007
A(119)	0.01
A(120)	0.007
A(121)	0.006
A(125)	0.01
A(126)	0.006
A(127)	0.13
A(128)	0.006
A(129)	0.004
A(130)	0.003
A(131)	0.002
A(132)	0.035
A(133)	0.005
A(19)	0.012
A(20)	0.009
A(28)	0.1
A(29)	0.017
A(64)	
A(65)	0.25
A(69)	0.015
A(70)	0.014
A(71)	0.009
A(72)	0.008
A(80)	0.022
A(81)	0.12
A(82)	0.035
A(83)	0.038
A(91)	0.16
A(92)	0.3
A(96)	0.011
B(1)	0.08
B(11)	0.26
B(12)	0.11
B(32)	0.091

B(33)	0.026
B(35)	0.01
B(36)	0.019
B(37)	0.022
B(38)	0.057
B(4)	0.006
B(5)	0.029
B(9)	0.006
A(102)	0.84
A(105)	0.25
A(135)	0.21
A(37)	6.8
A(83)	18.5
A(86)	31
A(87)	47
A(88)	12
A(73)	19% Inh @ 50uM
A(89)	27
A(90)	43
A(99)	8.4
B(10)	30
B(2)	46
B(3)	6.4
B(34)	1.3
B(5)	22
B(6)	12
B(7)	7
A(10)	0.003
A(11)	0.008
A(124)	0.008
A(14)	0.008
A(15)	0.007
A(16)	0.055
A(17)	0.016
A(18)	0.17
A(2)	0.82
A(27)	0.008
A(3)	0.001
A(33)	0.007
A(34)	0.012
A(35)	0.009
A(39)	0.03
A(38)	0.008
A(39)	0.008
A(4)	0.007
A(40)	0.012
A(41)	0.008

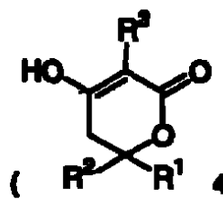
A(42)	0.004
A(43)	0.006
A(44)	0.007
A(45)	0.014
A(46)	0.006
A(48)	0.023
A(5)	8.6
A(51)	0.003
A(52)	0.003
A(53)	0.003
A(54)	0.005
A(55)	0.002
A(58)	0.004
A(6)	0.039
A(61)	0.14
A(62)	0.08
A(7)	11.3
A(8)	0.089
A(9)	0.005
B(29)	5.2
B(30)	1.2
B(31)	0.18
B(39)	0.012
A(100)	0.079
A(110)	0.006
A(112)	0.007
A(113)	0.007
A(122)	0.004
A(123)	0.039
A(134)	0.003
A(136)	0.003
A(137)	0.3
A(138)	0.01
A(139)	0.004
A(32)	0.005
A(60)	0.003
A(93)	0.006
B(13)	0.004
B(15)	0.019
B(16)	0.053
B(17)	0.026
B(21)	0.176
B(26)	18
B(27)	10
B(50)	0.043
B(51)	0.024
A(156)	0.005
A(157)	0.01

A(154)	0.011
A(155)	0.054

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We Claim:

1. A compound of formula (4),



(4)

wherein:

R^1 is cyclopentyl;

R^2 is $-(CR^6R^7)_n$(5-6 membered heterocyclic), wherein said 5-6 membered heterocyclic group is optionally substituted with at least one R^4 group;

R^3 is $-(CR^6R^7)_t(C_6-C_{10}$ aryl) or $-(CR^6R^7)_t$(4-10 membered heterocyclic), wherein each of said C_6-C_{10} aryl and 4-10 membered heterocyclic moieties of said R^3 groups are optionally substituted with at least one R^4 group;

each R^4 is independently selected from halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein said C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl groups are optionally substituted with at least one R^5;

each R^5 is independently selected from C_1-C_6 alkyl, halo, $-OR^6$, $-CF_3$, and -CN;

each R^6 and R^7 is independently selected from hydrogen and C_1-C_6 alkyl;

n is 0, 1, 2, 3, 4, or 5; and

t is 0, 1, 2, 3, 4, or 5; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that the compound of formula (4) is not 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, 3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-[2-(2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one, or 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethylpyridin-3-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one.

2. A compound according to claim 1, wherein n is 1 or 2 and t is 1 or 2.

3. A compound according to claim 2, wherein n is 2.

4. A compound according to claim 3, wherein R^2 is $-(CR^6R^7)_n$(4-10 membered heterocyclic), optionally substituted with at least one R^4 group.

5. A compound according to claim 4, wherein t is 1.

6. A compound according to claim 5, wherein R^3 is a $-(CH_2)_2$(pyridyl), $-(CH_2)_2$(pyrazolyl), $-(CH_2)_2$(pyrrolyl), $-(CH_2)_2$(oxazolyl), $-(CH_2)_2$(thiazolyl), $-(CH_2)_2$(imidazolyl), $-(CH_2)_2$(isoxazolyl),

–$(CH_2)_n$(isothiazolyl), –$(CH_2)_n$(1,2,3-triazolyl), –$(CH_2)_n$(1,3,4-triazolyl), –$(CH_2)_n$(1,3,4-thiadiazolyl), –$(CH_2)_n$(pyridazinyl), –$(CH_2)_n$(pyrimidinyl), –$(CH_2)_n$(pyrazinyl), or –$(CH_2)_n$(1,3,5-triazinyl) group, each of which is optionally substituted with at least one R^4 group.

7. A compound according to claim 6, wherein R^3 is –(CH_2)[1,2,4]triazolo[1,5-a]pyrimidin-2-yl), optionally substituted with at least one R^5 group.

8. A compound according to claim 7, wherein R^6 is –$(CH_2)_n$(pyridyl), –$(CH_2)_n$(pyrazolyl), or –$(CH_2)_n$(pyrrolyl), each of which is optionally substituted with at least one R^4 group;

9. A compound according to claim 8, wherein R^6 is –$(CH_2)_n$(pyridyl) or –$(CH_2)_n$(pyrazolyl), each of which is optionally substituted with at least one R^4 group.

10. A compound according to claim 9, wherein:

R^6 is –$(CH_2)_n$(pyridyl) or –$(CH_2)_n$(pyrazolyl), each of which is optionally substituted with at least one substituent selected from halo, C_1-C_6 alkyl, $-OR^6$, and $-NR^6R^7$; and

R^3 is –(CH_2)[1,2,4]triazolo[1,5-a]pyrimidin-2-yl), optionally substituted with at least one substituent selected from halo and C_1-C_6 alkyl.

11. A compound according to claim 10, wherein R^6 is –$(CH_2)_n$(pyridyl) optionally substituted with at least one substituent selected from halo, C_1-C_6 alkyl, $-OR^6$, and $-NR^6R^7$.

12. A compound according to claim 1, selected from:

6-[2-(6-amino-5-ethyl-2-methylpyridin-3-yl)ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(4-ethylpyridin-2-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-6-[2-(4-ethylpyridin-2-yl)ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-6-[2-(2,6-dimethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-(2-isopropylpyridin-4-yl)ethyl]-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-6-isopropylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-6-methylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-6-[2-(2-ethyl-6-methoxypyridin-4-yl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-propoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-6-[2-(2-ethyl-5-propoxypyridin-4-yl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;
6-[2-[2,6-bis(2,2,2-trifluoroethyl)pyridin-4-yl]ethyl]-6-cyclopentyl-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(6-ethyl-3-methoxypyridin-2-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(1-ethyl-1H-pyrazol-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-(1-isopropyl-1H-pyrazol-4-yl)ethyl]-5,6-dihydro-2H-pyran-2-one;
6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-[2-(5-methoxy-2-methylpyridin-4-yl)ethyl]-5,6-dihydro-2H-pyran-2-one;
6-[2-[2,6-bis(2,2,2-trifluoroethyl)pyridin-4-yl]ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
5-bromo-1-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)pyridin-2(1H)-one;
1-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)-5-ethylpyridin-2(1H)-one;
2-[3-chloro-5-(2-[2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl)pyridin-2-yl]-2-methylpropanenitrile;
(+)-6-[2-[2,6-bis(2,2,2-trifluoroethyl)pyridin-4-yl]ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(-)-6-[2-[2,6-bis(2,2,2-trifluoroethyl)pyridin-4-yl]ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(+)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

(-)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(+)-6-cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(-)-6-cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(+)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(-)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(+)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-propoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(-)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-propoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(+)-6-cyclopentyl-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one; and
(-)-6-cyclopentyl-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-3-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one; or
pharmaceutically acceptable salts or solvates thereof.

13. A compound according to claim 1, selected from:
(+)-6-[2-[2,6-bis(2,2,2-trifluoroethyl)pyridin-4-yl]ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(-)-6-[2-[2,6-bis(2,2,2-trifluoroethyl)pyridin-4-yl]ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(+)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(-)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(+)-6-cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(-)-6-cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(+)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;
(-)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

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(+)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-propoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

(-)-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-propoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one;

(+)-6-cyclopentyl-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one; and

(-)-6-cyclopentyl-6-[2-(5-ethoxy-2-ethylpyridin-4-yl)ethyl]-4-hydroxy-3-[(8-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-5,6-dihydro-2H-pyran-2-one; or pharmaceutically acceptable salts or solvates thereof.

14. A pharmaceutical composition, comprising a therapeutically effective amount of a compound according to any one of claims 1 to 13 and a pharmaceutically acceptable carrier.

15. A use of a compound according to any one of claims 1 to 13 in the preparation of a medicament for the treatment of a mammal suffering from infection with Hepatitis C virus.

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INHIBIDORES DE LA ARN POLIMERASA DEPENDIENTE DE ARN DEL VIRUS DE LA HEPATITIS C Y COMPOSICIONES Y TRATAMIENTOS QUE LOS USAN

Campo de la Invención

La presente invención se refiere a compuestos útiles como inhibidores de la enzima polimerasa del virus de la Hepatitis C, (HCV), a composiciones farmacéuticas que comprenden tales compuestos, a métodos de uso de tales compuestos y formulaciones en el tratamiento de mamíferos infectados por HCV, tales como seres humanos, y a métodos y compuestos intermedios útiles en la preparación de tales compuestos.

Antecedentes

La invención se refiere a agentes que inhiben la ARN polimerasa dependiente de ARN del virus de la hepatitis C (HCV) (RdRp). La invención también se refiere al uso de tales compuestos en composiciones farmacéuticas y a tratamientos terapéuticos útiles para inhibir la replicación del HCV.

HCV es un virus de ARN con envoltura que contiene un genoma de ARN monocatenario de sentido positivo con una longitud de aproximadamente 9,5 kb (Choo, et al., *Science* 244:359-362 (1989)). El genoma de ARN contiene una región 5' no traducida (5' NTR) de 341 nucleótidos (Brown, et al., *Nucl. Acids Res.* 20:5041-5045 (1992); Bukh, et al., *Proc. Natl. Acad. Sci. USA* 89:4942-4946 (1992)), una fase de lectura abierta (ORF) larga que codifica un solo polipéptido de 3.010 a 3.040 aminoácidos (Choo, et al. (1989), supra;*J*, y una región 3'-no codificante (3'-NTR) de longitud variable de aproximadamente 230 nucleótidos (Kolykhalov y col., J. *Virol.* 70:3363-3371 (1996); Tanaka, et al., *J. Virol.* 70:3307-3312 (1996)).

La 5' NTR es una de las regiones más conservadas del genoma viral y juega un papel central en el inicio de la traducción de la poliproteína viral. Una sola ORF codifica una poliproteína que se procesa en la traducción o después de la traducción en proteínas virales estructurales (nuclear, E1 y E2) y no estructurales (NS2, NS3, NS4A, NS4B, NS5A y NS5B) por proteinasas celulares o virales (Bartenschlager (1997), *supra)*. La 3' NTR contiene tres regiones distintas: una región variable de aproximadamente 38 nucleótidos después del codón stop de la poliproteína, un tracto de poliuridina de longitud variable con sustituciones intercaladas de citeínas, y 98 nucleótidos (nt) en el extremo 3' que están muy conservados entre diversos aislados de HCV. El orden de los genes dentro del genoma es: NH_2-C-E1-E2-p7-NS2-NS3NS4A-NS4B-NS5A-NS5B-COOH

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(Grakoui, et al., J. *Virol* 67:1385-1395 (1993)).

El virus de la hepatitis C (VHC) es un miembro del género hepacivirus de la familia *Flaviviridae*. Es el agente causante principal de la hepatitis viral no A no B y es el causante principal de la hepatitis asociada con las transfusiones y responde de una proporción significativa de casos de hepatitis en todo el mundo. Aunque la infección agua por HCV a menudo es asintomática, casi 80% de los casos progresa hasta hepatitis crónica. La propiedad de persistencia de la infección por HCV se ha explicado por su capacidad de escapar de la vigilancia inmune del hospedador por medio de una hipermutabilidad de las regiones expuestas en la proteína de la envoltura E2 (Weiner,,et al., *Virology* 180:842-848 (1991); Weiner, et al. *Proc. Natl. Acad. Sci. USA* 89.3468-3472

El procesamiento de las proteínas estructurales de la nucleocápsida (C), la proteína 1 y (E1, E2) de la envoltura y la región p7, está mediado por peptidasas señales del hospedador. Por el contrario, la maduración de la región no estructural (NS) se realiza por dos enzimas. La poliproteína de HCV primero se escinde por una peptidasa señal del hospedador que genera las proteínas estructurales C/E1, E1/E2, E2/p7 y p7/NS2 (Hijikata, et al., *Proc. Natl Acad. Sci. USA* 88:5547-5551 (1991); Lin, et al., J. *Virol.* 68:5063-5073 (1994)). La proteinasa NS2-3, que es una metaloproteasa, corta a continuación en la unión NS2/NS3. El complejo proteinasa NS3/4A (proteasa de serina NS3/cofactor NS4A), después corta en todos los sitios de escisión restantes (Bartenschlager, et al., J. *Virol.* 67:3835-3844 (1993); Bartenschlager, (1997), *supra).* Las actividades de helicasa de ARN y NTPasa también han sido identificadas en la proteína NS3. El tercio N-terminal de la proteína NS3 funciona como una proteasa, y los dos tercios restantes de la molécula actúan como una helicasa/ATPasa, que se cree que está implicada en la replicación de HCV (Bartenschlager, (1997), *supra).* NS5A puede fosforilarse y actuar como un supuesto cofactor de NS5B. La cuarta enzima viral, NS5B, es una ARN polimerasa dependiente de ARN (RdRp) y un componente clave responsable de la replicación del genoma de ARN viral (Lohmann, et al., J. *Virol.* 71:8416-8428 (1997)).

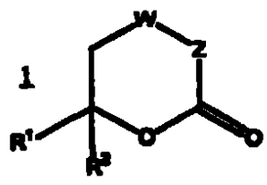
Se cree que la replicación de HCV se produce en complejos de replicación asociados a la membrana. Dentro de éstos, el ARN genómico de cadena positiva se transcribe en ARN de cadena negativa, que a su vez puede usarse como plantilla para la síntesis de cadenas genómicas positivas hijas. En esta reacción parecen estar implicadas dos proteínas virales: la proteína NS3, que lleva en los dos tercios del extremo carboxi una nucleósido trifosfatasa/ARN helicasa, y la proteína NS5B, que es una fosfo-

proteína asociada a la membrana con una actividad ARN polimerasa dependiente de ARN (RdRp) (Hwang, et al., J. *Virol.* 227:439-446 (1997)). Aunque el papel de NS3 en la replicación del ARN está menos claro, NS5B aparentemente es la enzima clave responsable de la síntesis de las cadena de ARN hijas. Usando baculovirus recombinantes para expresar NSSB en células de insectos y un ARN no viral sintético como sustrato, se han identificado dos actividades enzimáticas asociadas con NSSB. Las dos actividades incluyen una RdRp dependiente de cebador y una actividad transferasa terminal (TNTasa). La actividad de NSSB se confirmó y se caracterizó adicionalmente por medio del uso del genoma de ARN de HCV como sustrato (Lohmann, et al., *Virology* 249:108-118 (1998)). Ciertos estudios recientes han demostrado que NS5B con una truncación C-terminal de 21 aminoácidos expresada en *Escherichia coli* también es activa para la síntesis de ARN *in vitro* (Ferrari, et al., J. *Virol.* 73:1649-1654 (1999); Yamashita, et al., *J. Biol Chem.* 273:15479-15486 (1998)).

Puesto que la infección persistente con VHC está relacionada con la hepatitis crónica y, eventualmente, con la hepatocarcinogénesis, la replicación del VHC es uno de los objetivos para erradicar la reproducción del VHC y para evitar el carcinoma hepatocelular. Desafortunadamente, los enfoques del presente tratamiento para la infección por VHC se caracterizan por una eficacia relativamente mala y un perfil desfavorable de efectos secundarios. Por lo tanto, se dirige un gran esfuerzo al descubrimiento de moléculas para tratar esta enfermedad, incluyendo el descubrimiento de fármacos diseñados para inhibir la replicación de HC, ya que hay una necesidad persistente de compuestos de moléculas pequeñas, no peptídicos que son inhibidores de VHC RdRp que tienen propiedades físicas y químicas deseables o mejoradas apropiadas para aplicacion es farmacéuticas.

SUMARIO DE LA INVENCIÓN

La presente invención se refiere a compuestos de la fórmula 1



y a sales farmacéuticamente aceptables, hidratos, metabolitos, profármacos y solvatos

de los mismos, donde:

W-Z es -C(=O)-C(-R^3)(H)- o -C(-OR^6)=C(-$R^{3'}$)-, donde cuando W-Z es -C(-OR^6)=C(-$R^{3'}$)-;

cada R^1 se selecciona independientemente entre hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo (C_3-C_{10}), heterociclilo de 4 a 10 miembros, y arilo C_6-C_{10}, donde los grupos R^1 anteriores, excepto H, están opcionalmente sustituidos con 1 a 4 sustituyentes seleccionados entre R^4;

R^2 se selecciona entre el grupo de sustituyentes de R^1, -(CR^8R^9)$_t$(arilo C_6-C_{10}), -(CR^8R^9)$_t$(heterociclilo de 4 a 10 miembros), -(CR^8R^9)$_q$C(O)(CR^8R^9)$_t$(arilo C_6-C_{10}), -(CR^8R^9)$_q$C(O)(CR^8R^9)$_t$(heterociclilo de 4 a 10 miembros), -(CR^8R^9)$_t$O(CR^8R^9)$_q$(arilo C_6-C_{10}), -(CR^8R^9)$_t$O(CR^8R^9)$_q$(heterociclilo de 4 a 10 miembros), -(CR^8R^9)$_q$SO_n(CR^8R^9)$_t$(arilo C6-C_{10}) y -(CR^8R^9)$_q$SO_n(CR^8R^9)$_t$(heterociclilo de 4 a 10 miembros), donde cada uno de q y t es independientemente un número entero de 0 a 5, n es un número entero de 0 a 2, los restos alquilo, arilo y heterociclilo de dichos grupos R^2 están opcionalmente sustituidos con 1 a 5 grupos R^4 y con la condición de que R^2 no sea H;

R^3 es hidrógeno, -OR^6, -SR^6, -NR^6R^7 y el grupo de sustituyentes de R^2;

$R^{3'}$ se selecciona entre el grupo de sustituyentes de R^3 con la excepción de que $R^{3'}$ no es H;

cada R^4 se selecciona independientemente entre halo, ciano, nitro, trifluorometoxi, trifluorometilo, azido, alquilo C_1-C_{10}, alquenilo C_2-C_8, alquinilo C_2-C_8, -$C(O)R^6$, -$C(O)OR^6$, -$OC(O)R^6$, -$NR^6C(O)R^7$, -$NR^6C(O)NR^7$, -$C(O)NR^6R^7$, -NR^6R^7, -NR^6OR^7, -$SO_2NR^6R^7$, -$NR^6SO_2R^7$, -(CR^8R^9)$_t$(arilo C_6-C_{10}) (donde t es un número entero de 0 a 5), -(CR^8R^9)$_t$(heterociclilo de 4 a 10 miembros) (donde t es un número entero de 0 a 5), cicloalquilo C_3-C_{10}, R^6-O-, R^6SO_n- (donde n es un número entero de 0 a 2) y oxo (=O) y donde los restos alquilo, arilo y heterociclilo de dichos grupos R^4 están opcionalmente sustituidos con 1 a 4 sustituyentes seleccionados entre R^5;

cada R^5 se selecciona independientemente entre halo, trifluorometilo, trifluorometoxi, ciano, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_5, -OR^6, cicloalquilo C_3-C_{10}, arilo C_6-C_{10}, heterociclilo de 4 a 10 miembros, oxo (=O), -$C(O)R^6$, -$C(O)OR^6$, -$OC(O)R^6$, -$NR^6C(O)R^6$, -$NR^6C(O)NR^7$, -$C(O)NR^6R^7$, -NR^6R^7, -NR^6OR^7, -$NR^6SO_2R^7$ y -$SO_2NR^6R^7$, donde los restos alquilo, arilo y heterociclilo de los grupos R^5 anteriores están opcionalmente sustituidos con 1 a 3 R^{10};

cada uno de R^6 y R^7 se selecciona independientemente entre H, alquilo C_1-C_8, cicloalquilo C_3-C_{10}, -(CR^8R^9)$_t$(arilo C_6-C_{10}) y -(CR^8R^9)$_t$(heterociclilo de 4 a 10 miembros), donde t es un número entero de 0 a 5, 1 ó 2 átomos de carbono del anillo del grupo

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heterocíclico están opcionalmente sustituidos con un resto oxo (=O) y los restos alquilo, arilo y heterociclilo de los grupos R^6 y R^7 anteriores están opcionalmente sustituidos con 1 a 3 halo, ciano, trifluorometilo, trifluorometoxi, alquilo C_1-C_6, alcoxi C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, -$(CR^8R^9)_t$(arilo C_6-C_{10}) y -$(CR^8R^9)_t$(heterociclilo de 4 a 10 miembros), donde t es un número entero de 0 a 5;

cada uno de R^8 y R^9 se selecciona independientemente entre H y y alquilo C_1-C_4; y

cada R^{10} se selecciona independientemente entre halo, ciano, trifluorometilo, trifluorometoxi, -C(O)O-R^6, -OR^6, -C(O)$(CR^8R^9)_p$C(O)OR^6, donde p es un número entero de 1 a 5, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6 y -NR^6R^7.

La presente invención también se refiere a compuestos de fórmula (1), en la que:

W-Z es -C(=O)-C(-R^3)(H)- o-C(-OR^6)=C(-$R^{3'}$);

cada R^1 se selecciona independientemente entre hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo (C_3-C_{10}), heterociclilo de 4 a 10 miembros, y arilo C_6-C_{10}, donde los grupos R^1 anteriores, excepto H, están opcionalmente sustituidos con 1 a 4 sustituyentes seleccionados entre R^4;

R^2 se selecciona entre el grupo de sustituyentes de R^1, -$(CR^8R^9)_t$(cicloalquilo C_3-C_{10}), -$(CR^8R^9)_t$(arilo C_6-C_{10}), -$(CR^8R^9)_t$(heterociclilo de 4 a 10 miembros), -$(CR^8R^9)_qC(O)(CR^8R^9)_t$(arilo C_6-C_{10}), -$(CR^8R^9)_qC()(CR^8R^9)_t$(heterociclilo de 4 a 10 miembros), -$(CR^8R^9)_tO(CR^8R^9)_q$(arilo C_6-C_{10}), -$(CR^8R^9)_tO(CR^8R^9)_q$(heterociclilo de 4 a 10 miembros), -$(CR^8R^9)_qSO_n(CR^8R^9)_t$(arilo C_6-C_{10}) y -$(CR^8R^9)_qSO_n(CR^8R^9)_t$(heterociclilo de 4 a 10 miembros), donde cada uno de q y t es independientemente un número entero de 0 a 5, n es un número entero de 0 a 2, los restos alquilo, cicloalquilo, arilo y heterociclilo de dichos grupos R^2 están opcionalmente sustituidos con 1 a 5 grupos R^4 y con la condición de que R^2 no sea H;

R^3 es hidrógeno, -OR^6, -SR^6, -NR^8R^7 y el grupo de sustituyentes de R^2;

$R^{3'}$ se selecciona entre el grupo de sustituyentes de R^3;

cada R^4 se selecciona independientemente entre halo, ciano, nitro, trifluorometoxi, trifluorometilo, azido, alquilo C_1-C_{10}, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_{10}, -$(CR^8R^9)_tN(R^5)_2$, -$(CR^8R^9)_tNR^8C(O)R^8$, -$(CR^8R^9)_tOR^8$, -$(CR^8R^9)_tC(O)R^8$, -$(CR^8R^9)_tC(O)OR^8$, -$(CR^8R^9)_tC(O)R^8$, -$(CR^8R^9)_tNR^8C(O)R^7$, -$(CR^8R^9)_tNR^8C(O)OR^8$ -$(CR^8R^9)_tNR^8C(O)NR^7$, -$(CR^8R^9)_tC(O)NR^8R^7$, -$(CR^8R^9)_tNR^8R^7$, -$(CR^8R^9)_tNR^8OR^7$, -$(CR^8R^9)_tSO_2NR^8R^7$, -$(CR^8R^9)_tNR^8SO_2R^7$, -$(CR^8R^9)_t$(arilo C_6-C_{10})(donde t es un número entero de 0 a 5), -$(CR^8R^9)_t$(heterociclilo de 4 a 10 miembros) (donde t es un número

entero de 0 a 5), cicloalquilo C_3-C_{10}, R^8-O-, R^8-SO_n-$(CR^8R^9)_t$- (donde *n* es un número entero de 0 a 2) y oxo (=O) y donde los restos alquilo, arilo y heterociclilo de dichos grupos R^4 están opcionalmente sustituidos con 1 a 4 sustituyentes seleccionados entre R^8;

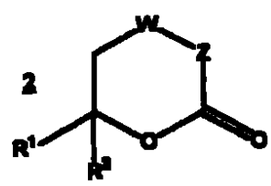
cada R^5 se selecciona independientemente entre halo, trifluorometilo, trifluorometoxi, ciano, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, $-OR^6$, cicloalquilo C_3-C_{10}, arilo C_6-C_{10}, heterociclilo de 4 a 10 miembros, oxo (=O), $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^6$, $-NR^6C(O)NR^7$, $-C(O)NR^6R^7$, NR^6R^7, $-NR^6OR^7$, $-NR^6SO_2R^7$ y $-SO_2NR^6R^7$, donde los restos alquilo, arilo y heterociclilo de los grupos R^5 anteriores están opcionalmente sustituidos con 1 a 3 R^{10};

cada uno de R^6 y R^7 se selecciona independientemente entre H, ciano, alquilo C_1-C_8, cicloalquilo C_3-C_{10}, $-(CR^8R^9)_t$(arilo C_6-C_{10}) y $-(CR^8R^9)_t$(heterociclilo de 4 a 10 miembros), $-(CR^8R^9)_tC(O)R^8$ donde t es un número entero de 0 a 5, 1 ó 2 átomos de carbono del anillo del grupo heterociclico están opcionalmente sustituidos con un resto (=O) y los restos alquilo, arilo y heterociclilo de los grupos R^6 y R^7 anteriores están opcionalmente sustituidos con 1 a 3 halo, ciano, cicloalquilo C_3-C_{10}, $-C(O)OR^8$, $-NR^8C(O)R^9$, $-(CR^8R^9)_tNR^8R^9$, $-OR^8$, $-NC(O)R^9$, trifluorometilo, trifluorometoxi, alquilo C_1-C_8, alcoxi C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, $-(CR^8R^9)_t$(arilo C_6-C_{10}) y $-(CR^8R^9)_t$(heterociclilo de 4 a 10 miembros), donde t es un número entero de 0 a 5;

cada uno de R^8 y R^9 se selecciona independientemente entre H y y alquilo C_1-C_4; y

cada R^{10} se selecciona independientemente entre halo, ciano, trifluorometilo, trifluorometoxi, $-C(O)OR^6$, $-C(O)O-R^6$, $-OR^6$, $-C(O)(CR^8R^9)_pC(O)OR^6$, donde p es un número entero de 1 a 5, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8 y $-NR^6R^7$.

La presente invención además se refiere a un compuesto de la fórmula **2**



y a sales farmacéuticamente aceptables, solvatos, metabolitos, profármacos y solvatos del mismo, donde:

W-Z es $-C(-OR^6)=C(-R^{3'})-$;

R^1 es ciclopentilo;

R^2 es $-(CR^8R^9)_t$(arilo C_6-C_{10}) o $-(CR^8R^9)_t$(heterociclilo de 4 a 10 miembros), donde t es un número entero de 0 a 5 y los restos arilo y heterociclilo de dichos grupos R^2 están opcionalmente sustituidos con 1 a 5 grupos R^4 y con la condición de que R^2 no sea H;

R^3 es hidrógeno, $-OR^6$, $-SR^6$, $-NR^6R^7$ y el grupo de sustituyentes de R^2;

cada R^4 se selecciona independientemente entre halo, ciano, nitro, trifluorometoxi, trifluorometilo, azido, alquilo C_1-C_{10}, alquenilo C_2-C_8, alquinilo C_2-C_8, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)NR^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-NR^6OR^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, $-(CR^8R^9)_t$(arilo C_6-C_{10}) (donde t es un número entero de 0 a 5), $-(CR^8R^9)_t$(heterociclilo de 4 a 10 miembros) (donde t es un número entero de 0 a 5), cicloalquilo C_3-C_{10}, R^6-O-, R^6-SO_n- (donde n es un número entero de 0 a 2) y oxo (=O) y donde los restos alquilo, arilo y heterociclilo de dichos grupos R^4 están opcionalmente sustituidos con 1 a 4 sustituyentes seleccionados entre R^5;

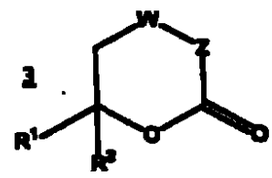
cada R^5 se selecciona independientemente entre halo, trifluorometilo, trifluorometoxi, ciano, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, $-OR^3$, cicloalquilo C_3-C_{10}, arilo C_6-C_{10}, heterociclilo de 4 a 10 miembros, oxo (=O), $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^6$, $-NR^6C(O)NR^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-NR^6OR^7$, $-NR^6SO_2R^7$ y $-SO_2NR^6R^7$, donde los restos alquilo, arilo y heterociclilo de los grupos R^5 anteriores están opcionalmente sustituidos con 1 a 3 R^{10};

cada uno de R^6 y R^7 se selecciona independientemente entre H, alquilo C_1-C_8, cicloalquilo C_3-C_{10}, $-(CR^8R^9)_t$(arilo C_6-C_{10}) y $-(CR^8R^9)_t$(heterociclilo de 4 a 10 miembros), donde t es un número entero de 0 a 5, 1 ó 2 átomos de carbono del anillo del grupo heterocíclico están opcionalmente sustituidos con un resto oxo (=O) y los restos alquilo, arilo y heterociclilo de los grupos R^6 y R^7 anteriores están opcionalmente sustituidos con 1 a 3 halo, ciano, trifluorometilo, trifluorometoxi, alquilo C_1-C_8, alcoxi C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, $-(CR^8R^9)_t$(arilo C_6-C_{10}) y $-(CR^8R^9)_t$(heterociclilo de 4 a 10 miembros), donde t es un número entero de 0 a 5;

cada uno de R^8 y R^9 se selecciona independientemente entre H y y alquilo C_1-C_4; y

cada R^{10} se selecciona independientemente entre halo, ciano, trifluorometilo, trifluorometoxi, $-C(O)O-R^8$, $-OR^8$, $-C(O)(CR^8R^9)_pC(O)OR^8$, donde p es un número entero de 1 a 5, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8 y $-NR^6R^7$.

La presente invención además se refiere a un compuesto de la fórmula (3)



y a sales farmacéuticamente aceptables, solvatos, profármacos y metabolitos del mismo, donde:

W-Z es -C(=O)-C(-R^3)(H)-;

R^1 es ciclopentilo;

R^2 es -(CR^8R^9)$_t$(arilo C_6-C_{10}) o -(CR^8R^9)$_t$(heterociclilo de 4 a 10 miembros), donde t es un número entero de 0 a 5 y los restos arilo y heterociclilo de dichos grupos R^2 están opcionalmente sustituidos con 1 a 5 grupos R^4 y con la condición de que R^2 no sea H;

R^3 es hidrógeno;

cada R^4 se selecciona independientemente entre halo, ciano, nitro, trifluorometoxi, trifluorometilo, azido, alquilo C_1-C_{10}, alquenilo C_2-C_8, alquinilo C_2-C_8, -$C(O)R^8$, -$C(O)OR^8$, -$OC(O)R^8$, -$NR^8C(O)R^7$, -$NR^8C(O)NR^7$, -$C(O)NR^8R^7$, -NR^8R^7, -NR^8OR^7, -$SO_2NR^8R^7$, -$NR^8SO_2R^7$, -(CR^8R^9)$_t$(arilo C_6-C_{10}) (donde t es un número entero de 0 a 5), -(CR^8R^9)$_t$(heterociclilo de 4 a 10 miembros) (donde t es un número entero de 0 a 5), cicloalquilo C_3-C_{10}, R^8-O-, R^8-SO_n- (donde n es un número entero de 0 a 2) y oxo (=O) y donde los restos alquilo, arilo y heterociclilo de dichos grupos R^4 están opcionalmente sustituidos con 1 a 4 sustituyentes seleccionados entre R^6;

cada R^5 se selecciona independientemente entre halo, trifluorometilo, trifluorometoxi, ciano, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, -OR^3, cicloalquilo C_3-C_{10}, arilo C_6-C_{10}, heterociclilo de 4 a 10 miembros, oxo (=O), -$C(O)R^8$, -$C(O)OR^8$, -$OC(O)R^8$, -$NR^8C(O)R^8$, -$NR^8C(O)NR^7$, -$C(O)NR^8R^7$, -NR^8R^7, -NR^8OR^7, -$NR^8SO_2R^7$ y -$SO_2NR^8R^7$, donde los restos alquilo, arilo y heterociclilo de los grupos R^5 anteriores están opcionalmente sustituidos con 1 a 3 R^{10};

cada uno de R^6 y R^7 se selecciona independientemente entre H, alquilo C_1-C_8, cicloalquilo C_3-C_{10}, -(CR^8R^9)$_t$(arilo C_6-C_{10}) y -(CR^8R^9)$_t$(heterociclilo de 4 a 10 miembros), donde t es un número entero de 0 a 5, 1 ó 2 átomos de carbono del anillo del grupo heterocíclico están opcionalmente sustituidos con un resto oxo (=O) y los restos alquilo, arilo y heterociclilo de los grupos R^8 y R^7 anteriores están opcionalmente sustituidos con 1 a 3 halo, ciano, trifluorometilo, trifluorometoxi, alquilo C_1-C_8, alcoxi C_1-C_8, alqueni-

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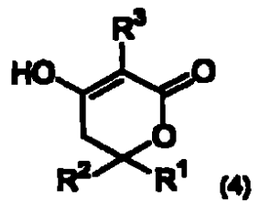
lo C_2-C_8, alquinilo C_2-C_8, -$(CR^8R^9)_t$(arilo C_6-C_{10}) y -$(CR^8R^9)_t$(heterociclilo de 4 a 10 miembros), donde t es un número entero de 0 a 5;

cada uno de R^8 y R^9 se selecciona independientemente entre H y y alquilo C_1-C_4; y

cada R^{10} se selecciona independientemente entre halo, cianо, trifluorometilo, trifluorometoxi, -C(O)O-R^6, -OR^6, -C(O)(CR^8R^9)pC(O)OR^6, donde p es un número entero de 1 a 5, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8 y -NR^6R^7.

En una realización específica de la presente invención, de acuerdo con la fórmula 1, R^2 es -$(CR^8R^9)_t$(arilo C_6-C_{10}), donde t es un número entero de 2 a 5 y el resto arilo de dicho grupo R^2 está opcionalmente sustituido con 1 a 5 grupos R^4 y con la condición de que R^2 no sea H; opcionalmente cada R^4 se selecciona independientemente entre halo, nitro, alquilo C_1-C_{10}, -C(O)R^6, -C(O)OR^6, -$OC(O)R^6$, -C(O)NR^6R7, -$(CR^8R^9)_t$(heterociclilo de 4 a 10 miembros) (donde t es un número entero de 0 a 5), cicloalquilo C_3-C_{10}, R^6-O- y donde los restos alquilo, arilo y heterociclilo de dichos grupos R^4 están opcionalmente sustituidos con 1 a 4 sustituyentes seleccionados entre R^5, opcionalmente cada R^5 se selecciona independientemente entre halo, trifluorometilo, alquilo C_1-C_8, -OR^6, cicloalquilo C_3-C_{10}, arilo C_6-C_{10}, oxo (=O), -C(O)R^6, -C( )OR^6, -$OC(O)R^6$, -$NR^6C(O)R^6$, -$NR^6C(O)NR^7$, -C(O)NR^6R^7, -NR^6R^7, -NR^6OR^7, -$NR^6SO_2R^7$ y -$SO_2NR^6R^7$, donde los restos alquilo y arilo de los grupos R^5 anteriores están opcionalmente sustituidos con 1 a 3 R^{10}; opcionalmente cada R^{10} se selecciona independientemente entre halo, trifluorometilo, -C(O)O-R^6, -OR^6, alquilo C_1-C_8 y NR^6R^7; opcionalmente R^3 es -OR^6, -SR^6, -NR^6R^7 y -$(CR^8R^9)_t$(arilo C_6-C_{10}), donde t es un número entero de 2 a 5 y el resto arilo de dicho grupo R^2 está opcionalmente sustituido con 1 to 5 grupos R^4.

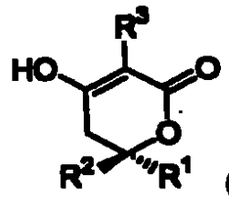
En otro aspecto de la presente invención se proporcionan compuestos de fórmula (4),



(4)

donde cualquiera de las definiciones de R^1, R^2 y R^3 son como se indica más adelante.

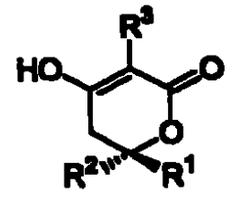
Además se proporcionan compuestos de fórmula (4a),



(4a)

donde cualquiera de las definiciones de R^1, R^2 y R^3 son como se indica más adelante.

Además se proporcionan compuestos de fórmula (4b),



(4b)

donde cualquiera de las definiciones de R^1, R^2 y R^3 son como se indica más adelante.

En esta invención, se contempla específicamente que los compuestos de fórmula (4) incluyen tanto a los compuestos de fórmula (4a) como (4b), a menos que se indique otra cosa.

En un aspecto adicional se proporcionan compuestos de fórmula (4) en la que:

R^1 es ciclopentilo;

R^2 es $-(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo heterocíclico de 5 a 6 miembros está opcionalmente sustituido con al menos un grupos R^4;

R^3 es $-(CR^6R^7)_t$(arilo C_6-C_{10}) o $-(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros), donde cada uno de dichos restos arilo C_6-C_{10} y heterociclilo de 4 a 10 miembros de dichos grupos R^3 están opcionalmente sustituidos con al menos un grupo R^5;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde cada grupo alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 está opcionalmente sustituido con al menos un R^5;

cada R^5 se selecciona independientemente entre alquilo C_1-C_6, halo, $-OR^6$, $-CF_3$ y -CN;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

n es 0. 1, 2, 3, 4, ó 5; y

t es 0, 1, 2, 3, 4, ó 5; o

sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, 3-[(6-cloro[1,2,4]triazolo(1,5-a]pirimidin-2-il)metil]-6-ciclopentil-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, o 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etilpiridin-3-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona.

Otro aspecto más de la presente invención proporciona compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es $-(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo heterocíclico de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

R^3 es $-(CR^6R^7)_t$(arilo C_6-C_{10}) o $-(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros), donde dichos restos arilo y heterociclilo de dichos grupos R^3 están opcionalmente sustituidos con al menos un grupo R^5;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

cada R^5 se selecciona independientemente entre alquilo C_1-C_6, halo, $-OR^6$, $-CF_3$ y -CN;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

n es 1 o 2; y

t es 1 o 2; o

sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, 3-[(6-cloro[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-ciclopentil-6-[2-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, o 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil-6-[2-(5-etilpiridin-3-il)etil]-4-hidroxi-5,6-

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dihidro-2H-piran-2-ona.

Además, se proporcionan compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es $-(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo heterocíclico de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

R^3 es $-(CR^6R^7)_t$(arilo C_6-C_{10}) o $-(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros), donde dichos restos arilo y heterociclilo de dichos grupos R^3 están opcionalmente sustituidos con al menos un grupo R^5;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

cada R^5 se selecciona independientemente entre alquilo C_1-C_6, halo, $-OR^6$, $-CF_3$ y -CN;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C6;

n es 2; y

t es 1 o 2; o

sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, 3-[(6-cloro[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-ciclopentil-6-2-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, o 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil-6-[2-(5-etilpiridin3-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona.

En otro aspecto más se proporcionan compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es $-(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo heterocíclico de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

R^3 es $-(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros), opcionalmente sustituido con al menos un grupo R^5;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$,

-CN, -C(O)R^6, -C(O)OR^6, -OC(O)R^6, -NR^6C(O)R^7, -NR^6C(O)OR^7, -NR^6C(O)NR^6R^7, -C(O)NR^6R^7, -SO_2NR^6R^7, -N$R^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

cada R^5 se selecciona independientemente entre alquilo C_1-C_6, halo, -OR^6, -CF_3 y -CN;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

n es 2; y

t es 1 o 2; o

sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, 3-[(6-cloro[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-ciclopentil-6-2-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, o 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil-6-[2-5-etilpiridin3-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona.

En este documento además se proporcionan compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es -$(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo heterocíclico de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

R^3 es -$(CR^6R^7)_n$(heterociclilo de 4 a 10 miembros), opcionalmente sustituido con al menos un grupo R^5;

cada R^4 se selecciona independientemente entre halo, -OR^6, oxo, -NR6R^7, -CF_3, -CN, -C(O)R^6, -C(O)OR^6, -OC(O)R^6, -NR^6C(O)R^7, -NR^6C(O)OR^7, -NR^6C(O)NR^6R^7, -C(O)NR^6R^7, -SO_2NR^6R^7, -N$R^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

cada R^5 se selecciona independientemente entre alquilo C_1-C_6, halo, -OR^6, -CF_3 y -CN;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

n es 2; y

t es 1; o

sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, 3-((6-cloro[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-ciclopentil-6-[2-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro2H-piran-2-ona, o 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il]metil-6-[2-(5-etilpiridin3-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona.

Otro aspecto adicional proporciona compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es un grupo $-(CH_2)_2$(piridilo), $-(CH_2)_2$(pirazolilo), $-(CH_2)_2$(pirrolilo), $-(CH_2)_2$(oxazolilo), $-(CH_2)_2$(tiazolilo), $-(CH_2)_2$(imidazolilo), $-(CH_2)_2$(isoxazolilo), $-(CH_2)_2$(isotiazolilo), $-(CH_2)_2$(1,2,3-triazolilo), $-(CH_2)_2$(1,3,4-triazolilo), $-(CH_2)_2$(1,3,4-tiadiazolilo), $-(CH_2)_2$(piridazinilo), $-(CH_2)_2$(pirimidinilo), $-(CH_2)_2$(pirazinilo), o $(CH_2)_2$(1,3,5-triazinilo), cada uno de los cuales está opcionalmente sustituido con al menos un grupo R^4;

R^3 es $-(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros), opcionalmente sustituido con al menos un grupo R^5;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

cada R^5 se selecciona independientemente entre alquilo C_1-C_6, halo, -OR6, $-CF_3$ y -CN;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6; y

t es 1 o 2; o

sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, 3-[(6-cloro[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-ciclopentil-6-[2-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, o 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etilpiridin-3-il)etil]-4-hidroxi-5,6-

dihidro-2H-piran-2-ona.

Además se proporcionan compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es un grupo - $(CH_2)_2$(piridilo), -$(CH_2)_2$(pirazolilo), -$(CH_2)_2$(pirrolilo), -$(CH_2)_2$(oxazolilo), -$(CH_2)_2$(tiazolilo), -$(CH_2)_2$(imidazolilo), -$(CH_2)_2$(isoxazolilo), -$(CH_2)_2$(isotiazolilo), -$(CH_2)_2$(1,2,3-triazolilo), -$(CH_2)_2$(1,3,4-triazolilo), -$(CH_2)_2$(1,3,4-tiadiazolilo), -$(CH_2)_2$(piridazinilo), -$(CH_2)_2$(pirimidinilo), -$(CH_2)_2$(pirazinilo), o $CH_2)_2$(1,3,5-triazinilo), cada uno de los cuales está opcionalmente sustituido con al menos un grupo R^4;

R^3 es -(CH_2)(heterociclilo de 4 a 10 miembros), opcionalmente sustituido con al menos un grupo R^5;

cada R^4 se selecciona independientemente entre halo, -OR^6, oxo, -NR^6R^7, -CF_3, -CN, -$C(O)R^6$, -$C(O)OR^6$, -$OC(O)R^6$, -$NR^6C(O)R^7$, -$NR^6C(O)OR^7$, -$NR^6C(O)NR^6R^7$, -$C(O)NR^6R^7$, -$SO_2NR^6R^7$, -$NR_6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^6;

cada R^5 se selecciona independientemente entre alquilo C_1-C_6, halo, -OR^6, -CF_3 y -CN y

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6; o

sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, 3-[(6-cloro[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-ciclopentil-6-[2-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro2H-piran-2-ona, o 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil-6-[2-(5-etilpiridin-3-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona.

Otro aspecto adicional proporciona compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es un grupo -$(CH_2)_2$(piridilo), -(CH2)$_2$(pirazolilo), -$(CH_2)_2$(pirrolilo), -$(CH_2)_2$(oxazolilo), -$(CH_2)_2$(tiazolilo), -$(CH_2)_2$(imidazolilo), -$(CH_2)_2$(isoxazolilo), -$(CH_2)_2$(isotiazolilo), -$(CH_2)_2$(1,2,3-triazolilo), -$(CH_2)_2$(1,3,4-triazolilo), -$(CH_2)_2$(1,3,4-tiadiazolilo), -$(CH_2)_2$(piridazinilo), -$(CH_2)_2$(pirimidinilo), -$(CH_2)_2$(pirazinilo), o -$(CH_2)_2$(1,3,5-

triazinilo), cada uno de los cuales está opcionalmente sustituido con al menos un grupo R^4;

R^3 es -(CH_2)([1,2,4]triazolo[1,5-a]pirimidin-2-ilo), opcionalmente sustituido con al menos un grupo R^5;

cada R^4 se selecciona independientemente entre halo, -OR^6, oxo, -NR^6R^7, -CF_3, -CN, -$C(O)R^6$, -$C(O)OR^6$, -$OC(O)R^6$, -$NR^6C(O)R^7$, -$NR^6C(O)OR^7$, -$NR^6C(O)NR^6R^7$, -$C(O)NR^6R^7$, -$SO_2NR^6R^7$, -$NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

cada R^5 se selecciona independientemente entre alquilo C_1-C_6, halo, -OR^6, -CF_3 y -CN y

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_5; o

sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, 3-[(6-cloro[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-ciclopentil-6-[2-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro2H-piran-2-ona, o 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil-6-[2-(5-etilpiridin-3-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona.

Otro aspecto adicional más proporciona compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es un grupo -$(CH_2)_2$(piridilo), -$(CH_2)_2$(pirazolilo), -$(CH_2)_2$(pirrolilo), -(CH2)2(oxazolilo), -$(CH_2)_2$(tiazolilo), -$(CH_2)_2$(imidazolilo), -$(CH_2)_2$(isoxazolilo), -$(CH_2)_2$(isotiazolilo), -$(CH_2)_2$(1,2,3-triazolilo), -$(CH_2)_2$(1,3,4-triazolilo), -$(CH_2)_2$(1,3,4-tiadiazolilo), -$(CH_2)_2$(piridazinilo), -$(CH_2)_2$(pirimidinilo), -$(CH_2)_2$(pirazinilo), o -$(CH_2)_2$(1,3,5-triazinilo), cada uno de los cuales está opcionalmente sustituido con al menos un grupo R^4;

R^3 es -(CH_2)([1,2,4]triazolo[1,5-a]pirimidin-2-ilo), opcionalmente sustituido con al menos un grupo R^5;

cada R^4 se selecciona independientemente entre halo, -OR^6, oxo, -NR^6R^7, -CF_3, -CN, -$C(O)R^6$, -$C(O)OR^6$, -$OC(O)R^6$, -$NR^6C(O)R^7$, -$NR^6C(O)OR^7$, -$NR^6C(O)NR^6R^7$, -$C(O)NR^6R^7$, -$SO_2NR^6R^7$, -$NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

mente sustituidos con al menos un R^5;

cada R^5 se selecciona independientemente entre alquilo C_1-C_6, halo, $-OR^6$, $-CF_3$ y -CN y

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6; o

sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, 3-[(6-cloro[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-ciclopentil-6-[2-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro2H-piran-2-ona, o 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil-6-[2-(5-etilpiridin-3-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona.

Otro aspecto adicional más son compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es $-(CH_2)_2$(piridilo) o $-(CH_2)_2$(pirazolilo), cada uno de los cuales está opcionalmente sustituido con al menos un grupo R^4;

R^3 es $-(CH_2)$([1,2,4]triazolo[1,5-a]pirimidin-2-ilo), opcionalmente sustituido con al *menos un grupo* R^5;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C8, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

cada R^5 se selecciona independientemente entre alquilo C_1-C_6, halo, $-OR^6$, $-CF_3$ y -CN y

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6; o

sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, 3-[(6-cloro[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-ciclopentil-6-[2-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro2H-piran-2-ona, o 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil-6-[2-(5-etilpiridin-3-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona.

Otro aspecto más, son compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es $-(CH_2)_2$(piridilo) o $-(CH_2)_2$(pirazolilo), cada uno de los cuales está opcionalmente sustituido con al menos un sustituyente seleccionado entre halo, alquilo C_1-C_6, $-OR^6$ y $-NR^6R^7$;

R^3 es $-(CH_2)$([1,2,4]triazolo[1,5-a]pirimidin-2-ilo), opcionalmente sustituido con al menos un sustituyente seleccionado entre halo y alquilo C_1-C_6; y

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6; o

sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, 3-[(6-cloro[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-ciclopentil-6-[2-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, o 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil-6-[2-(5-etilpiridin-3-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona.

Otro aspecto adicional más proporciona compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es $-(CH_2)_2$(piridilo) opcionalmente sustituido con al menos un sustituyente seleccionado entre halo, alquilo C_1-C_6, $-OR^6$ y $-NR^6R^7$;

R^3 es $-(CH_2)$([1,2,4]triazolo[1,5-a]pirimidin-2-ilo), opcionalmente sustituido con al menos un sustituyente seleccionado entre halo y alquilo C_1-C_6; y

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6; o

sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, 3-[(6-cloro[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-ciclopentil-6-[2-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro2H-piran-2-ona, o 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil-6-[2-(5-etilpiridin-3-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona.

Además se proporcionan compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es -$(CH_2)_2$(pirazolilo) opcionalmente sustituido con al menos un sustituyente seleccionado entre halo, alquilo C_1-C_6, -OR^6 y -NR^6R^7;

R^3 es -(CH_2)([1,2,4]triazolo[1,5-a]pirimidin-2-ilo), opcionalmente sustituido con al menos un sustituyente seleccionado entre halo y alquilo C_1-C_6; y

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6; o

sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil]-6-2-(2-etilpiridin-4-il)etil-4-hidroxi-5,6-dihidro-2H-piran-2-ona, 3-((6-cloro[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-ciclopentil-6-[2-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro2H-piran-2-ona, o 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il]metil-6-[2-(5-etilpiridin3-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona.

Otro aspecto adicional más son compuestos seleccionados entre:

6-[2-(6-amino-5-etil-2-metilpiridin-3-il)etil]-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(4-etilpiridin-2-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(4-etilpiridin-2-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]-triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(2,6-dietilpiridin-4-il)etil]-3-[(5,7-dimetil[1,2,4]triazolo-[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(2,6-dimetilpiridin-4-il)etil]-3-[(5,7-dimetil[1,2,4]triazolo-[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-metoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-[2-(2isopropilpiridin-4-il)etil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-6-isopropilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2-(2-etil-6-

metilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(2,6-dietilpiridin-4-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]-triazolo[1,5-a]pirimidin2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(2-etil-5-metoxipiridin-4-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-propoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-3-[(6-metil-[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(2-etil-5-propoxipiridin-4-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-[2-[2,6-bis(2,2,2-trifluoroetil)piridin-4-il]etil]-6-ciclopentil-4-hidroxi-3-((6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(6-etil-3-metoxipiridin-2-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo(1,5-a]pirimidin-2-il)metil]-6-[2-(1-etil-1H-pirazol-4il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-[2-(1-isopropil-1H-pirazol-4-il)etil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-[2-(5-metoxi-2-metilpiridin-4-il)etil]-5,6-dihidro-2H-piran-2-ona;

6-[2-[2,6-bis(2,2,2-trifluoroetil)piridin-4-il]etil]-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

5-bromo-1-(2-(2-ciclopentil-5-[(5,7-dimetil(1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)piridin-2(1H)-ona;

1-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6dihidro-2H-piran-2-il}etil)-5-etilpiridin-2(1H)-ona;

2-[3-cloro-5-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)piridin-2-il]-2-metilpropanonitrilo;

(+)-6-{2-[2,6-bis(2,2,2-trifluoroetil)piridin-4-il]etil)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(-)-6-{2-[2,6-bis(2,2,2-trifluoroetil)piridin-4-il]etil)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(+)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo(1,5-a]pirimidin-2-il)metil-6-[2-(2-etil-5-metoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(-)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-metoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(+)-6-ciclopentil-6-[2-(2,6-dietilpiridin-4-il)etil]-3-[(5,7-dimetil[1,2,4]-triazoto[1,5-a]pirimidin-2-il)metil)-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(-)-6-ciclopentil-6-[2-(2,6-dietilpiridin-4-il)etil]-3-[(5,7-dimetil[1,2,4]-triazolo[1,5-a]pirimidin-2il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(+)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(-)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(+)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-propoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(-)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-propoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(+)-6-ciclopentil-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-3-[(6-metil-[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona y

(-)-6-ciclopentil-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-3-[(6-metil-[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona; o

sus sales y solvatos farmacéuticamente aceptables.

Un aspecto adicional de la presente invención proporciona compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es $-(CR^6R^7)_n$(arilo C_6-C_{10}) o $-(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros), donde cada uno de dichos grupos arilo $_{C6}$-C_{10} y heterociclilo de 4 a 10 miembros está opcionalmente sustituido con al menos un grupo R^4;

R^3 es $-(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros) sustituido con al menos un R^5 y además opcionalmente sustituido con al menos un alquilo C_1-C_6;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, $-CN$, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde cada uno de dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 está opcionalmente sustituido con al menos un R^5;

R^6 es halógeno, oxo, cicloalquilo C_3-C_6, arilo C_6-C_{10}, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$ y heterociclilo de 4 a 10 miembros sustituido con R^6;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

n es 0, 1, 2, 3, 4, ó 5; y

t es 0, 1, 2, 3, 4, ó 5; o

sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-[2-[4-(benciloxi)fenil]etil]-6-ciclopentil-3-[(2-ciclopropil-6-hidroxipirimidin-4-il)metil]dihidro-2H-piran-2,4(3H)-diona, {5-[(6-ciclopentil-6-[2-[4-(difluorometil)-3-fluorofenil]etil]-2,4-dioxotetrahidro-2H-piran-3-il)metil]isoxazol-3-il}carbamato de metilo; o 6-[2-(5-cloro-2,4-dimetoxifenil)etil]-6-ciclopentil-3-[(3-piridin-2-il-1,2,4-oxadiazol-5-il)metil]dihidro-2H-piran-2,4(3H)-diona.

En otro aspecto más, se proporcionan compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es $-(CR^6R^7)_n$(arilo C_6-C_{10}) o $-(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros), donde de cada uno de dichos grupos arilo C_6-C_{10} y heterociclilo de 4 a 10 miembros está opcionalmente sustituido con al menos un grupo R^4;

R^3 es $-(CH_2)$(heterociclilo de 4 a 10 miembros) sustituido con al menos un R^5 y además opcionalmente sustituido con al menos un alquilo C_1-C_6;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, $-CN$, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

R^5 es halógeno, oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$ y heterociclilo de 4 a 10 miembros sustituido con R^6;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

n es 0, 1, 2, 3, 4, ó 5; y

t es 0, 1, 2, 3, 4, ó 5; o

sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-(2-[4-(benciloxi)fenil]etil)-6-ciclopentil-3-(2-ciclopropil-6-hidroxipirimidin-4-il)metil]dihidro-2H-piran-2,4(3H)-diona, {5-[(6-ciclopentil-6-{2-[4-(difluorometil)-3-fluorofenil]etil}-2,4-dioxotetrahidro-2H-piran-3-il)metil]isoxazol-3-il}carbamato de metilo; o 6-[2-(5-cloro-2,4-dimetoxifenil)etil]-6-ciclopentil-3-[(3-piridin-2-il-1,2,4-oxadiazol-5-il)metil]dihidro-2H-piran-2,4(3H)-diona.

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Además se proporcionan compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es $-(CH_2)_z$(arilo C6-C_{10}) o $-(CH_2)_z$(heterociclilo de 4 a 10 miembros), donde cada uno de dichos grupos arilo C_6-C_{10} y heterociclilo de 4 a 10 miembros está opcionalmente sustituido con al menos un grupo R^4;

R^3 es $-(CH_2)$(heterociclilo de 4 a 10 miembros) sustituido con al menos un R^8 y además opcionalmente sustituido con al menos un alquilo C_1-C_6;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde cada uno de dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 está opcionalmente sustituido con al menos un R^5;

R^8 es halógeno, oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$ y heterociclilo de 4 a 10 miembros sustituido con R^6;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

n es 0, 1, 2, 3, 4, ó 5; y

t es 0, 1, 2, 3, 4, ó 5; o

cada uno de sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-[2-[4-(benciloxi)fenil]etil]-6-ciclopentil-3-[(2-ciclopropil-6-hidroxipirimidin-4-il)metil]dihidro-2H-piran-2,4(3H)-diona, {5-[(6-ciclopentil-6-(2-[4-(difluorometil)-3-fluorofenil]etil}-2,4-dioxotetrahidro-2H-piran-3-il)metil]isoxazol-3-il}carbamato de metilo; o 6-[2-(5-cloro-2,4-dimetoxifenil)etil]6-ciclopentil-3-[(3-piridin-2-il-1,2,4-oxadiazol-5-il)metil]dihidro-2H-piran-2,4(3H)-diona.

Además, se proporcionan compuestos seleccionados entre:

2-[4-(2-(2-ciclopentil-5-[(1,5-dimetil-3-oxo-2-fenil-2,3-dihidro-1H-pirazol-4-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo;

2-[(6-[2-(3-cloro-4-(1-ciano-1-metiletil)fenil]etil}-6-ciclopentil-4-hidroxi-2-oxo-5,6-dihidro-2H-piran-3-il)metil][1,2,4]triazolo[1,5-a]pirimidina-6-carboxilato de etilo;

6-[2-(5-cloro-2,4-dimetoxifenil)etil]-6-ciclopentil-4-hidroxi-3-[(1-metil-3-pirazin-2-il-1H-1,2,4-triazol-5-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-(2-(5-cloro-2,4-dimetoxifenil)etil]-6-ciclopentil-4-hidroxi-3-[(1-metil-3-piridin-2-il-1H-1,2,4-triazol-5-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-[2-(5-cloro-2,4-dimetoxifenil)etil]-6-ciclopentil-4-hidroxi-3-[(1-metil-3-fenil-1H-1,2,4-triazol-5-il)metil]-5,6-dihidro-2H-piran-2-ona;

2-{4-[2-(2-ciclopentil-4-hidroxi-5-[[1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-il]metil]-6-oxo-3,6-dihidro-2H-piran-2-il)etil]-2-fluorofenil}2-metilpropanonitrilo;

2-{4-[2-(2-ciclopentil-5-([1,3-dimetil-5-(4-metilpiperazin-1-il)-1H-pirazol-4-il]metil}-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil]-2-fluorofenil}2-metilpropanonitrilo;

2-[4-(2-{2-ciclopentil-4-hidroxi-5-[(1-metil-3-pirazin-2-il-1H-1,2,4-triazol-5-il)metil]-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo;

2-[4-(2-{2-ciclopentil-5-[(3-etil-1-metil-5-morfolin-4-il-1H-pirazol-4-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo;

2-[4-(2-{2-ciclopentil-5-[(1,3-dimetil-5-morfolin-4-il-1H-pirazol-4-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo; y

2-{4-[2-(2-ciclopentil-5-([3-(difluorometil)-5-(dimetilamino)-1-metil-1H-pirazol-4-il]metil}-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil]-2-fluorofenil}-2-metilpropanonitrilo;

o

sus sales y solvatos farmacéuticamente aceptables.

En un aspecto adicional más de la presente invención, se proporcionan compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es $-(CR^6R^7)_n$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está sustituido con al menos un grupo R^{4a} y está opcionalmente sustituido con al menos un grupo R^{4b};

R^3 es $-(CR^6R^7)_t$(arilo C_6-C_{10}) o $-(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros), donde dichos restos arilo y heterociclilo de dichos grupos R^3 están opcionalmente sustituidos con al menos un grupo R^5;

cada R^{4a} se selecciona independientemente entre -O(heterociclilo de 4 a 10 miembros), -S(heterociclilo de 4 a 10 miembros) y $-(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros);

cada R^{4b} se selecciona independientemente entre halo, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_8, alquenilo C_2-C_8 y alquinilo C_2-C_8, donde dichos grupos alquilo C_1-C_8, alquenilo C_2-C_8 y alquinilo C_2-C_8 están opcionalmente sustituidos con al menos un R^8;

cada R^5 se selecciona independientemente entre alquilo C_1-C_8, halo, $-OR^6$, $-CF_3$ y -CN;

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cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

n es 0, 1, 2, 3, 4, ó 5; y

t es 0, 1, 2, 3, 4, ó 5; o

sus sales y solvatos farmacéuticamente aceptables.

Otro aspecto proporciona compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es -$(CH_2)_2$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está sustituido con al menos un grupo R^{4a} y está opcionalmente sustituido con al menos un grupo R^{4b};

R^3 es -$(CR^6R^7)_t$(arilo C_6-C_{10}) o -$(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros), donde dichos restos arilo y heterociclilo de dichos grupos R^3 están opcionalmente sustituidos con al menos un grupo R^5;

cada R^{4a} se selecciona independientemente entre -O(heterociclilo de 4 a 10 miembros), -S(heterociclilo de 4 a 10 miembros) y -$(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros);

cada R^{4b} se selecciona independientemente entre halo, oxo, -NR^6R^7, -CF_3, -CN, -$C(O)R^6$, -$C(O)OR^6$, -$OC(O)R^6$, -$NR^6C(O)R^7$, -$NR^6C(O)OR^7$, -$NR^6C(O)NR^6R^7$, -$C(O)NR^6R^7$, -$SO_2NR^6R^7$, -$NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

cada R^5 se selecciona independientemente entre alquilo C_1-C_6, halo, -OR^6, -CF_3 y -CN;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6; y

t es 0, 1, 2, 3, 4, ó 5; o

sus sales y solvatos farmacéuticamente aceptables.

En este documento además se proporcionan compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es -$(CH_2)_2$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está sustituido con al menos un grupo R^{4a} y está opcionalmente sustituido con al menos un grupo R^{4b};

R^3 es -(CH_2)(arilo C_6-C_{10}) o -(CH_2)(heterociclilo de 4 a 10 miembros), donde dichos restos arilo y heterociclilo de dichos grupos R^3 están opcionalmente sustituidos

con al menos un grupo R^5;

cada R^{4a} se selecciona independientemente entre -O(heterociclilo de 4 a 10 miembros), -S(heterociclilo de 4 a 10 miembros) y -$(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros);

cada R^{4b} se selecciona independientemente entre halo, oxo, -NR^6R^7, -CF_3, -CN, -$C(O)R^6$, -$C(O)OR^6$, -$OC(O)R^6$, -$NR^6C(O)R^7$, -$NR^6C(O)OR^7$, -$NR^6C(O)NR^6R^7$, -$C(O)NR^6R^7$, -$SO_2NR^6R^7$, -$NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

cada R^5 se selecciona independientemente entre alquilo C_1-C_6, halo, -OR^6, -CF_3 y -CN;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6; y

t es 0 ó 1; o

sus sales y solvatos farmacéuticamente aceptables.

En este documento, además se proporcionan compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es -$(CH_2)_2$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está sustituido con al menos un grupo R^{4a} y está opcionalmente sustituido con al menos un grupo R^{4b};

R^3 es -(CH_2)(heterociclilo de 4 a 10 miembros), donde dichos restos arilo y heterociclilo de dichos grupos R^3 están opcionalmente sustituidos con al menos un grupo R^5;

cada R^{4a} se selecciona independientemente entre -O(heterociclilo de 4 a 10 miembros), -S(heterociclilo de 4 a 10 miembros) y -$(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros);

cada R^{4b} se selecciona independientemente entre halo, oxo, -NR^6R^7, -CF_3, -CN, -$C(O)R^6$, -$C(O)OR^6$, -$OC(O)R^6$, -$NR^6C(O)R^7$, -$NR^6C(O)OR^7$, -$NR^6C(O)NR^6R^7$, -$C(O)NR^6R^7$, -$SO_2NR^6R^7$, -$NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

cada R^5 se selecciona independientemente entre alquilo C_1-C_6, halo, -OR^6, -CF_3 y -CN;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alqui-

lo C_1-C_6; y

t es 0 ó 1; o

sus sales y solvatos farmacéuticamente aceptables.

En otro aspecto más, se proporcionan compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es -$(CH_2)_2$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está sustituido con al menos un grupo R^{4a} y está opcionalmente sustituido con al menos un grupo R^{4b};

R^3 es -(CH_2)([1,2,4]triazolo[1,5-a]pirimidin-2-ilo), opcionalmente sustituido con al menos un sustituyente seleccionado entre halo y alquilo C_1-C_6;

cada R^{4a} se selecciona independientemente entre -O(heterociclilo de 4 a 10 miembros), -S(heterociclilo de 4 a 10 miembros) y -$(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros);

cada R^{4b} se selecciona independientemente entre halo, oxo, -NR^6R^7, -CF_3, -CN, -$C(O)R^6$, -$C(O)OR^6$, -$OC(O)R^6$, -$NR^6C(O)R^7$, -$NR^6C(O)OR^7$, -$NR^6C(O)NR^6R^7$, -$C(O)NR^6R^7$, -$SO_2NR^6R^7$, -$NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

cada R^5 se selecciona independientemente entre alquilo C_1-C_6, halo, -OR^6, -CF_3 y -CN;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6; y

t es 0 ó 1; o

sales farmacéuticamente aceptables o solvatos de los mismos.

Otro aspecto adicional más son compuestos de fórmula (4), en la que:

R^1 es ciclopentilo;

R^2 es -$(CH_2)_2$(arilo C_6-C_{10}), donde dicho grupo arilo C6-C_{10} está sustituido con al menos un grupo R_{4a} y está opcionalmente sustituido con al menos un grupo R^{4b};

R^3 es -(CH_2)([1,2,4]triazolo[1,5-a]pirimidin-2-ilo), sustituido con al menos un sustituyente seleccionado entre halo y alquilo C_1-C_6;

cada R^{4a} se selecciona independientemente entre -O(heterociclilo de 4 a 10 miembros), -S(heterociclilo de 4 a 10 miembros) y -$(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros);

cada R^{4b} se selecciona independientemente entre halo, oxo, -NR^6R^7, -CF_3, -CN,

$-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

cada R^5 se selecciona independientemente entre alquilo C_1-C_6, halo, $-OR^6$, $-CF_3$ y -CN;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6; y

t es 0 ó 1; o

sus sales y solvatos farmacéuticamente aceptables.

Además se proporcionan compuestos seleccionados entre:

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-(3-etil-4-(1H-1,2,4triazol-1-ilmetil)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-[3-etil-4-(1H-pirazol-1-ilmetil)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-{2-[3-etil-4-(1H-pirazol-1-ilmetil)fenil]etil}-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2-[3-etil- 4-(1,3-tiazol-2-iloxi)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-[3-etil-4-(morfolin-4-ilmetil)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona,

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-[3-etil-4-(1,3-oxazol-2-il)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-{2-[3-etil-4-(1,3-oxazol-2-il)fenil]etil}-4-hidroxi-3-([1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil)-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-{2-(3-etil-4-(1,3-oxazol-2-il)fenil)etil}-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

(+)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-[3-etil-4-(1,3oxazol-2-il)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(-)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil]-6-{2-[3-etil-4-(1,3oxazol-2-il)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona; y

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-(2-[3-etil-4-(pirrolidin-1-ilmetil)fenil]etil)-4-hidroxi-5,6-dihidro-2H-piran-2-ona; o

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En otro aspecto más de la presente invención, se proporcionan compuestos seleccionados entre:

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etil-4-hidroxi-2-propoxifenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6dihidro-2H-piran-2-il}etil)-2-etilfenil]acetonitrilo;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]6-[2-(3-etil-4-metilfenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(6R)-6-ciclopentil-6-[2-(5-etil-2,4-dihidroxifenil)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo(1,5-a]pirimidin-2-il)metil]-6-[2-(2-etoxi-5-etil-4-hidroxifenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-((5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-[2-(4-metoxi-3-(trifluorometil)fenil]etil}-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etil-2,4-dimetoxifenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(2-etoxi-5-etil-4-hidroxifenil)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2-(5-etil-4-hidroxi-2-isopropoxifenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxifenil)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2-(5-etil-2-hidroxi-4-propoxifenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(5-etil-2-hidroxi-4-propoxifenil)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etil-4-hidroxi-2-isobutoxifenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-[2-[4-hidroxi-3-metil-5-(2,2,2-trifluoroetil)fenil]etil}-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-(2-[4-hidroxi-2-propoxi-5-(2,2,2-trifluoroetil)fenil]etil}-5,6-dihidro-2H-piran-2-ona;

2-[4-(2-{2-ciclopentil-4-hidroxi-5-[(6-metil[1,2,4]pirazolo[1,5-a]pirimidin-2-il)metil]-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-metilfenil]-2-metilpropanonitrilo;

2-[4-(2-{2-ciclopentil-5-((1,3-dimetil-1H-1,2,4-triazol-5-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo;

2-[4-(2-{2-ciclopentil-5-[(1-etil-1H-pirazol-4-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo;

2-[4-(2-{2-ciclopentil-4-hidroxi-5-[(1-metil-1H-pirazol-4-il)metil]-6-oxo-3,6-dihidro-2H-piran-2il}etil)-2-fluorofenil]-2-metilpropanonitrilo;

2-(4-(2-{2-ciclopentil-4-hidroxi-6-oxo-5-[(1,3,5-trimetil-1H-pirazol-4-il)metil]-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo;

2-[4-(2-{2-ciclopentil-5-[(1,5-dimetil-1H-pirazol-4-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo;

2-[4-(2-(2-ciclopentil-5-[(1-etil-3-metil-1H-pirazol-4-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo;

2-(4-(2-{5-[(5-cloro-1,3-dimetil-1H-pirazol-4-il)metil]-2-ciclopentil-4-hidroxi-6-oxo-3,6-dihidro2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo;

2-(4-(2-(5-[[5-cloro-1-metil-3-(trifluorometil)-1H-pirazol-4-il]metil]-2-ciclopentil-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil]-2-fluorofenil}-2-metilpropanonitrilo;

2-(2-cloro-4-(2-[2-ciclopentil-4-hidroxi-5-(imidazo[1,2-b][1,2,4]triazin-6-ilmetil)-6-oxo-3,6-dihidro-2H-piran-2-il]etil}fenil)-2-metilpropanonitrilo;

6-[2-(5-cloro-2,4-dimetoxifenil)etil]-6-ciclopentil-3-((1-etil-3,5-dimetil-1H-pirazol-4-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-[2-(3-cloro-4-isopropoxifenil)etil]-6-ciclopentil-3-((1-etil-3,5-dimetil-1H-pirazol-4-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

2-[4-(2-{2-ciclopentil-5-[(2-etil-5-oxo-5H-[1,3,4]tiadiazolo[3,2-a]pirimidin-7-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo;

2-[2-cloro-4-(2-(2-ciclopentil-5-[(1,3-dimetil-1H-1,2,4-triazol-5-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)fenil]-2-metilpropanonitrilo;

2-[2-cloro-4-(2-{2-ciclopentil-5-((1-etil-1H-pirazol-4-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)fenil]-2-metilpropanonitrilo;

2-[2-cloro-4-(2-{2-ciclopentil-4-hidroxi-5-[(1-metil-1H-pirazol-4-il)metil]-6-oxo-3,6-dihidro-2Hpiran-2-il}etil)fenil]-2-metilpropanonitrilo;

2-[2-cloro-4-(2-{2-ciclopentil-4-hidroxi-6-oxo-5-[(1,3,5-trimetil-1H-pirazol-4-il)metil]-3,6-dihidro-2H-piran-2-il}etil)fenil]-2-metilpropanonitrilo;

2-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6dihidro-2H-piran-2-il}etil)-2-(trifluorometil)fenil]-2-metilpropanonitrilo;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-[2-

[4-hidroxi-3-(trifluorometil)fenil]etil]-5,6-dihidro-2H-piran-2-ona;

2-[4-(2-(2-ciclopentil-4-hidroxi-5-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluoro-5-hidroxifenil]-2-metilpropanonitrilo;

[4-(2-(2-ciclopentil-4-hidroxi-5-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilfenil]acetonitrilo;

[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-(trifluorometil)fenil]acetonitrilo;

2-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-(trifluorometil)fenil]-2-etilbutanonitrilo;

2-(4-(2-(2-ciclopentil-5-[(3-etil-1-metil-1H-1,2,4-triazol-5-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo;

2-[4-(2-(2-ciclopentil-5-[(1-etil-3,5-dimetil-1H-pirazol-4-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-fluorofenil]-2-metilpropanonitrilo; y

2-[4-(2-(2-ciclopentil-5-[(1-etil-5-metil-1H-1,2,4-triazol-3-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo; o

sus sales y solvatos farmacéuticamente aceptables.

En otro aspecto más de la presente invención, se proporcionan compuestos seleccionados entre:

(+)-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilfenil]acetonitrilo;

(-)-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilfenil]acetonitrilo;

(+)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etil-4-hidroxi-2,3-dihidro-1-benzofuran-7-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(-)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etil-4-hidroxi-2,3-dihidro-1-benzofuran-7-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(+)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etoxi-5-etil-4-hidroxifenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(-)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etoxi-5-etil-4-hidroxifenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(+)-6-ciclopentil-6-[2-(2-etoxi-5-etil-4-hidroxifenil)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

(-)-6-ciclopentil-6-[2-(2-etoxi-5-etil-4-hidroxifenil)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

(+)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-{2-[4-hidroxi-3-(2,2,2-trifluoroetil)fenil]etil}-5,6-dihidro-2H-piran-2-ona; y

(-)-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-{2-[4-hidroxi-3-(2,2,2-trifluoroetil)fenil]etil}-5,6-dihidro-2H-piran-2-ona; o

sus sales y solvatos farmacéuticamente aceptables.

Además, la presente invención comprende compuestos seleccionados entre:

N-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilfenil]metanosulfonamida; N-[4(2-{2-ciclopentil-4-hidroxi-5-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilfenil]metanosulfonamida;

N-(4-{2-[2-ciclopentil-4-hidroxi-6-oxo-5-([1,2,4]triazolo(1,5-a]pirimidin-2-ilmetil)-3,6-dihidro-2H-piran-2-il]etil}-2-etilfenil)metanosulfonamida;

N-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilfenil]etanosulfonamida;

N-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilfenil]propano-1-sulfonamida;

4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilbenzoato de metilo;

6-ciclopentil-6-(2-{4-[(dimetilamino)metil]-3-etilfenil}etil)-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-[3-etil-4-(metoximetil)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etil-N-metilbenzamida;

6-[2-[4-(aminometil)-3-etilfenil]etil]-6-ciclopentil-3-[(5,7-dimetil[1,2,4]-triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilbencilcarbamato de terc-butilo;

6-ciclopentil-6-[2-(4-[[(ciclopropilmetil)amino]metil}-3-etilfenil)etil]-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

N-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilbencil]metanosulfonamida;

N-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilbencil]acetamida;

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6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo(1,5-a]pirimidin-2-il)metil-6-{2-[5-etil-2-(3-metoxipropil)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2-[3-etil-4-(3-metoxipropil)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

N-{4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6dihidro-2H-piran-2-il}etil)-2-fluorobencil]acetamida;

N-{1-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-1-metiletil}metanosulfonamida;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-[4-(etilsulfonil)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-(2-{4-[(trifluorometil)sulfonil]fenil}etil)-5,6-dihidro-2H-piran-2-ona;

2-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilfenoxi]etil-(metil)carbamato de terc-butilo;

2-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilfenoxi]-etilcarbamato de terc-butilo;

6-[2-[4-(2-aminoetoxi)-3-etilfenil[etil]-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2-(3-etil-4-[2-(metilamino)etoxi]fenil}etil)-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-[5-fluoro-4-(hidroximetil)-2-metoxifenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

N-{(1R)-1-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)fenil]etil}-etanosulfonamida;

N-{(1R)-1-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo(1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)fenil]etil}-2,2,2-trifluoroetanosulfonamida;

N-{(1R)-1-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)fenil]etil}-metanosulfonamida;

(1R)-1-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)fenil]-etilcarbamato de terc-butilo;

6-(2-(4-[(1R)-1-aminoetil]fenil}etil)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]-triazolo[1,5-a]pirimidin-2-il)metil]-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-[2-(5-acetil-4-hidroxi-2-metoxifenil)etil]-6-ciclopentil-3-[(5,7-dimetil-

[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-(2-[3-cloro-4-(metilsulfonil)fenil]etil}-6-ciclopentil-3-[(5,7-dimetil-[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

ácido 4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorobenzoico;

ácido 2-cloro-4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)benzoico;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-{2-[4-(1-hidroxi-1-metiletil)-3-metilfenil]etil}-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-[3-etil-4-(hidroximetil)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-(2-[3-cloro-4-(1-hidroxi-1-metiletil)fenil]etil)-6-ciclopentil-4-hidroxi-3-([1,2,4]triazolo[1,5a]pirimidin-2-ilmetil)-5,6-dihidro-2H-piran-2-ona;

6-{2-[3-cloro-4-(1-hidroxi-1-metiletil)fenil]etil}-6-ciclopentil-4-hidroxi-3-[(6-metil[1,2,4]triazolo(1,5-a)pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-{2-[3-cloro-4-(1-hidroxi-1-metiletil)fenil]etil}-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-{2-[3-cloro-4-(1-hidroxi-1-metiletil)fenil]etil}-3-[(6-cloro[1,2,4]-triazolo[1,5-a]pirimidin-2-il)metil]-6-ciclopentil-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-{2-[4-(metilsulfonil)-3-(trifluorometil)fenil]etil}-5,6-dihidro-2H-piran-2-ona;

4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorobenzoato de metilo; y

2-cloro-4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)benzoato de metilo; o

sus sales y solvatos farmacéuticamente aceptables.

En otro aspecto más, se proporcionan compuestos seleccionados entre:

(+)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-[3-etil-4-(hidroximetil)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(-)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-[3-etil-4-(hidroximetil)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

(+)-N-[4-(2-{2-ciclopentil-5-((5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilbencil]-metanosulfonamida;

(-)-N-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-

hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilbencil]-metanosulfonamida;

(+)-N-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilbencil]acetamida;

(-)-N-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilbencil]acetamida;

(+)-6-ciclopentil-6-(2-{4-[(dimetilamino)metil]-3-etilfenil}etil)-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona; y

(-)-6-ciclopentil-6-(2-{4-[(dimetilamino)metil]-3-etilfenil}etil)-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona; o

sus sales y solvatos farmacéuticamente aceptables.

Además se proporcionan compuestos seleccionados entre:

{4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-etilfenil}-acetonitrilo;

N-{4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-etilfenil}-metanosulfonamida;

6-ciclopentil-6-[2-[3-etil-4-(1,3-oxazol-2-il)fenil]etil]dihidro-2H-piran-2,4(3H)-diona;

N-((1R)-1-{4-(2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]fenil}-etil)etanosulfonamida;

6-ciclopentil-6-[2-[3-fluoro-4-(metilsulfonil)fenil]etil}dihidro-2H-piran-2,4(3H)-diona;

6-ciclopentil-6-(2-{4-[(trifluorometil)sulfonil]fenil}etil)dihidro-2H-piran-2,4(3H)-diona;

2-{4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-etilfenoxi}etil(metil)carbamato de terc-butilo;

2-(4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-etilfenoxi}etilcarbamato de terc-butilo;

2-{4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-etil-5-metoxifenoxi}etil(metil)carbamato de terc-butilo;

N-((1R)-1-{4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]fenil}-etil)-2,2,2-trifluoroetanosulfonamida;

(1R)-1-{4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-fenil}etilcarbamato de terc-butilo;

6-[2-(5-acetil-4-hidroxi-2-metoxifenil)etil]-6-ciclopentildihidro-2H-piran-2,4(3H)-diona;

ácido 2-cloro-4-(2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]benzoico;

6-[2-[3-cloro-4-(metilsulfonil)fenil]etil]-6-ciclopentildihidro-2H-piran-2,4(3H)-diona;

6-ciclopentil-6-[2-[4-(metilsulfonil)-3-(trifluorometil)fenil]etil]dihidro-2H-piran-2,4(3H)-diona;

6-ciclopentil-6-[2-[3-etil-4-(hidroximetil)fenil]etil]dihidro-2H-piran-2,4(3H)-diona;

4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-fluorobenzoato de metilo;

ácido 4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-fluorobenzoico;

2-cloro-4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-benzoato de metilo;

2-[4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-(trifluorometil)fenil]-2-metilpropanonitrilo;

[4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-(trifluorometil)-fenil]acetonitrilo;

1-[4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-(trifluorometil)fenil]ciclopropanocarbonitrilo;

2-[4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-(trifluorometil)fenil]-2-etilbutanonitrilo;

4-[4-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)butil]piperidina-1-carboxilato de terc-butilo;

6-ciclopentil-6-[2-(2-etil-5-metoxipiridin-4-il)etil]dihidro-2H-piran-2,4(3H)-diona;

6-ciclopentil-6-[2-(6-etil-3-metoxipiridin-2-il)etil]dihidro-2H-piran-2,4(3H)-diona;

6-ciclopentil-6-[2-(5-metoxi-2-metilpiridin-4-il)etil]dihidro-2H-piran-2,4(3H)-diona;

y

2-[3-cloro-5-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]piridin-2-il]-2-metilpropanonitrilo; o

sales farmacéuticamente aceptables o solvatos de los mismos.

La presente invención además proporciona compuestos seleccionados entre:

6-ciclopentil-6-[2-[2-(ciclopropilmetoxi)-5-etil-4-hidroxifenil]etil]-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-[2-[2-(ciclobutilmetoxi)-5-etil-4-hidroxifenil]etil]-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

1-[4-(2-[2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-

hidroxi-6-oxo-3,6dihidro-2H-piran-2-il}etil)fenil]ciclopropanocarbonitrilo;

3-[(2-amino-7H-purin-6-il)tio]-6-[2-(5-cloro-2,4-dimetoxifenil)etil]-6-ciclopentildihidro-2Hpiran-2,4(3H)-diona;

2-[2-cloro-4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)(metil)amino]-4,6-dioxotetrahidro-2H-piran-2-il}etil)fenil]-2-metilpropanonitrilo;

2-[2-cloro-4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)oxi]-4,6-dioxotetrahidro-2H-piran-2-il}etil)fenil]-2-metilpropanonitrilo;

1-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-(trifluorometil)fenil]-ciclopropanocarbonitrilo;

4-(4-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}butil)piperidina-1-carboxilato de terc-butilo; y

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-(4-piperidin-4-ilbutil)-5,6-dihidro-2H-piran-2-ona; o

sus sales y solvatos farmacéuticamente aceptables.

La invención también se refiere a un método para el tratamiento del virus de la Hepatitis C (HCV) en un mamífero, tal como un ser humano, que comprende administrar a dicho mamífero una cantidad de un compuesto de la presente invención o una sal o solvato del mismo que sea eficaz en el tratamiento de HCV.

En otro aspecto de la presente invención, se proporcionan métodos para el tratamiento de un mamífero, tal como un ser humano, que padece una infección con el virus de la Hepatitis C, que comprende administrar a dicho mamífero una cantidad inhibidora del virus de la Hepatitis C de un compuesto de la presente invención o una sal farmacéuticamente aceptable, profármaco, metabolito farmacéuticamente activo o solvato del mismo.

La presente invención también se refiere a un método de inhibición de la polimerasa de la Hepatitis C, que comprende poner en contacto dicha polimerasa con una cantidad para inhibir la polimerasa de un compuesto de la presente invención, o una sal farmacéuticamente aceptable, profármaco, metabolito farmacéuticamente activo o solvato del mismo.

La presente invención también se refiere a una composición farmacéutica para el tratamiento del virus de la Hepatitis C (HCV) en un mamífero, tal como un ser humano, que comprende una cantidad de un compuesto de la presente invención, o una sal farmacéuticamente aceptable, profármaco, metabolito farmacéuticamente activo o sol-

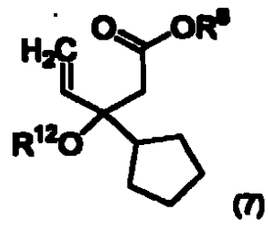
vato del mismo, que es eficaz para tratar el virus de la Hepatitis C en un animal infectado y un vehículo farmacéuticamente aceptable.

La presente invención también se refiere a la inhibición de la replicación del virus de la Hepatitis C en un mamífero, tal como un ser humano, que comprende administrar a dicho mamífero una cantidad inhibidora de la replicación del virus de la Hepatitis C de un compuesto de la presente invención.

La presente invención también se refiere a un método para inhibir la actividad de la proteína RdRp del virus de la Hepatitis C, que comprende poner en contacto la proteína con una cantidad eficaz de un compuesto de la presente invención, o una sal farmacéuticamente aceptable del mismo, profármaco, metabolito farmacéuticamente activo o solvato del mismo. Por ejemplo, la actividad HCV puede inhibirse en el tejido de mamíferos por medio de la administración de un agente inhibidor de HCV de acuerdo con la invención.

La presente invención también se refiere al uso de los compuestos de la invención en la preparación de un medicamento para el tratamiento de un mamífero que padece una infección por el virus de la Hepatitis C. El medicamento puede comprender una cantidad inhibidora del virus de la Hepatitis C de un compuesto o compuestos de la invención y un vehículo o vehículos farmacéuticamente aceptables.

En un aspecto adicional de la presente invención se proporcionan compuestos de fórmula (7),



(7)

en la que:

R^8 es hidrógeno o alquilo C_1-C_8;

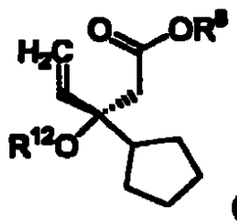
R^{12} es hidrógeno o -C(O)R^{13}; y

R^{13} es alquilo C_1-C_8 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_8, -OH, -OCH_3 y -N(alquilo C_1-C_8)$_2$;

o una sal de los mismos.

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Además, en este documento se proporcionan compuestos de fórmula (7a),



(7a)

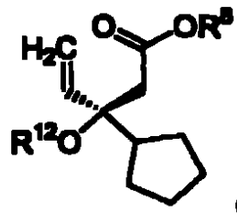
R^8 es hidrógeno o alquilo C_1-C_8;

R^{12} es hidrógeno o $-C(O)R^{13}$; y

R^{13} es alquilo C_1-C_8 o $-(CH_2)$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_8, -OH, $-OCH_3$ y $-N$(alquilo C_1-C_8)$_2$;

o una sal de los mismos.

En otro aspecto adicional más se proporcionan compuestos de fórmula (7b),



(7b)

R^8 es hidrógeno o alquilo C_1-C_8;

R^{12} es hidrógeno o $-C(O)R^{13}$; y

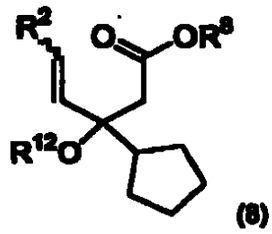
R^{13} es alquilo C_1-C_8 o $-(CH_2)$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_8, -OH, $-OCH_3$ y $-N$(alquilo C_1-C_8)$_2$;

o una sal de los mismos.

En otro aspecto adicional más se proporciona cualquiera de los compuestos anteriores de fórmula (7), (7a), o (7b), donde R^8 es hidrógeno o cualquiera de los compuestos en los que R^8 es alquilo C_1-C_8.

En este documento además se proporcionan compuestos de fórmula (8),

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(8)

en la que:

R^2 es $-(CR^6R^7)_n$arilo C_6-C_{10} o $-(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo arilo C_6-C_{10} o heterociclilo de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, $-CN$, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

R^5 es oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, $-CN$ y heterociclilo de 4 a 10 miembros sustituido con R^6;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

R^8 es hidrógeno o alquilo C_1-C_6;

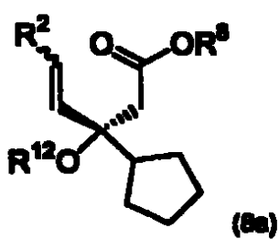
R^{12} es hidrógeno o $-C(O)R^{13}$;

R^{13} es alquilo C_1-C_6 o $-(CH_2)$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, $-OH$, $-OCH_3$ y $-N$(alquilo C_1-C_6)$_2$; y

n es 0, 1, 2, 3, 4, o 5;

o una sal de los mismos.

En un aspecto adicional más se proporcionan compuestos de fórmula (8a),



(8a)

en la que:

R^2 es $-(CR^6R^7)_n$arilo C_6-C_{10} o $-(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo arilo C_6-C_{10} o heterociclilo de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, $-CN$, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

R^5 es oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, $-CN$ y heterociclilo de 4 a 10 miembros sustituido con R^6;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

R^8 es hidrógeno o alquilo C_1-C_6; y

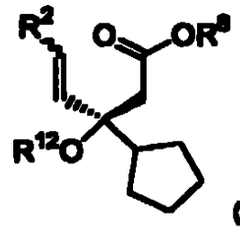
R^{12} es hidrógeno o $-C(O)R^{13}$;

R^{13} es alquilo C_1-C_6 o $-(CH_2)$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, $-OH$, $-OCH_3$ y $-N$(alquilo C_1-C_6)$_2$; y

n es 0, 1, 2, 3, 4, o 5;

o una sal de los mismos.

En este documento además se proporcionan compuestos de fórmula (8b),



(8b)

en la que:

R^2 es $-(CR^6R^7)_n$(arilo C_6-C_{10}) o $-(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo arilo C_6-C_{10} o heterociclilo de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$,

-CN, -C(O)R^8, -C(O)OR^8, -OC(O)R^8, -NR^8C(O)R^7, -NR^8C(O)OR^7, -NR^8C(O)NR^8R^7, -C(O)NR^8R^7, -SO_2NR^8R^7, -NR^8SO_2R^7, alquilo C_1-C_8, alquenilo C_2-C_8 y alquinilo C_2-C_8, donde dichos grupos alquilo C_1-C_8, alquenilo C_2-C_8 y alquinilo C_2-C_8 están opcionalmente sustituidos con al menos un R^5;

R^5 es oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, -OR^6, -C(O)OR^6, -NR^6R^7, -CN y heterociclilo de 4 a 10 miembros sustituido con R^6,

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_8;

R^8 es hidrógeno o alquilo C_1-C_8; y

R^{12} es hidrógeno o -C(O)R^{13};

R^{13} es alquilo C_1-C_8 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_8, -OH, -OCH_3 y -N(alquilo C_1-C_8)$_2$; y

n es 0, 1, 2, 3, 4, o 5;

o una sal de los mismos.

Además, en este documento está incluido cualquier compuesto de la (8), (8a), o (8b) anteriores, donde:

R^2 es -(CR^8R^7)$_n$arilo C_6-C_{10}, opcionalmente sustituido con al menos un grupo R^4;

cada R^4 se selecciona independientemente entre halo, -OR^8, oxo, -NR^8R^7, -CF_3, -CN, -C(O)R^8, -C(O)OR^8, -OC(O)R^8, -NR^8C(O)R^7, -NR^8C(O)OR^7, -NR^8C(O)NR^8R^7, -C(O)NR^8R^7, -SO_2NR^8R^7, -NR^8SO_2R^7, alquilo C_1-C_8, alquenilo C_2-C_8 y alquinilo C_2-C_8, donde dichos grupos alquilo C_1-C_8, alquenilo C_2-C_8 y alquinilo C_2-C_8 están opcionalmente sustituidos con al menos un R^5;

R^5 es oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, -OR^6, -C(O)OR^6, -NR^6R^7, -CN y heterociclilo de 4 a 10 miembros sustituido con R^6;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_8;

R^8 es hidrógeno o alquilo C_1-C_8; y

R^{12} es hidrógeno o-C(O)R^{13};

R^{13} es alquilo C_1-C_8 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_8, -OH, -OCH_3 y -N(alquilo C_1-C_8)$_2$; y

n es 0, 1, 2, 3, 4, o 5;

o una sal de los mismos.

Además, en este documento está incluido cualquier compuesto de fórmula (8), (8a), o (8b) anteriores, donde:

R^2 es arilo C_6-C_{10} sustituido con al menos un sustituyente seleccionado entre halo, $-OR^6$, $-CF_3$, -CN y alquilo C_1-C_8, donde dicho alquilo C_1-C_8 está opcionalmente sustituido con al menos un R^5;

R^5 es oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, $-OR^8$, $-C(O)OR^8$, $-NR^8R^7$, -CN y heterociclilo de 4 a 10 miembros sustituido con R^6,

cada uno de R^8 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_8; y

R^6 es hidrógeno o alquilo C_1-C_8;

R^{12} es hidrógeno o $-C(O)R^{13}$; y

R^{13} es alquilo C_1-C_8 o $-(CH_2)$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_8, -OH, $-OCH_3$ y -N(alquilo C_1-C_8)$_2$;

o una sal de los mismos.

Además, en este documento está incluido cualquier compuesto de la (8), (8a), o (8b) anteriores, donde:

R^2 es arilo C_6-C_{10} sustituido con halo y $-C(CH_3)_2CN$; y

R^6 es hidrógeno o alquilo C_1-C_8; y

R^{12} es hidrógeno;

o una sal de los mismos.

Además, en este documento está incluido cualquier compuesto de fórmula (8), (8a), o (8b) anteriores, donde:

R^2 es arilo C_6-C_{10} sustituido con flúor y $-C(CH_3)_2CN$; y

R^6 es hidrógeno o alquilo C_1-C_8; y

R^{12} es hidrógeno;

o una sal de los mismos.

Además, en este documento está incluido cualquier compuesto de la (8), (8a), o (8b) anteriores, donde:

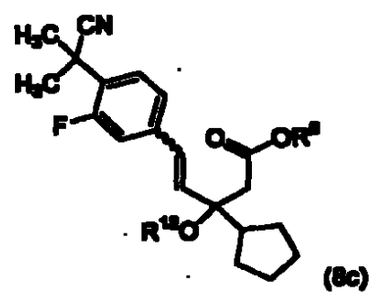
R^2 es arilo C_6-C_{10} sustituido con cloro y $-C(CH_3)_2CN$; y

R^6 es hidrógeno o alquilo C_1-C_8; y

R^{12} es hidrógeno;

o una sal de los mismos.

La presente invención además proporciona compuestos de fórmula (8c),



(8c)

en la que:

R^5 es hidrógeno o alquilo C_1-C_6;

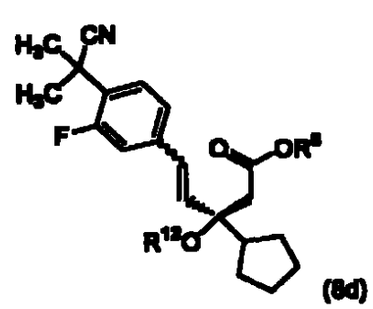
R^{12} es hidrógeno o -C(O)R^{13}; y

R^{13} es alquilo C_1-C_6 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$;

o una sal de los mismos.

En este documento además se proporcionan compuestos de fórmula (8c), en la que R^{12} es hidrógeno; o una sal de los mismos.

En otro aspecto de la presente invención se proporcionan compuestos de fórmula (8d),



(8d)

en la que:

R^8 es hidrógeno o alquilo C_1-C_6;

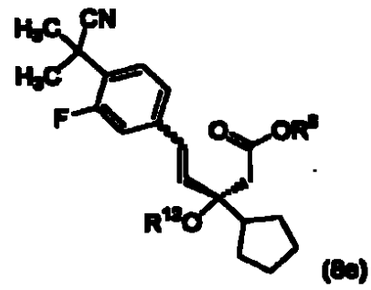
R^{12} es hidrógeno o -C(O)R^{13}; y

R^{13} es alquilo C_1-C_6 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$;

o una sal de los mismos.

Además, en este documento se proporcionan compuestos de fórmula (8d), en la que R^{12} es hidrógeno; o una sal de los mismos.

La presente invención además proporciona compuestos de fórmula (8e),



(8e)

en la que:

R^8 es hidrógeno o alquilo C_1-C_6;

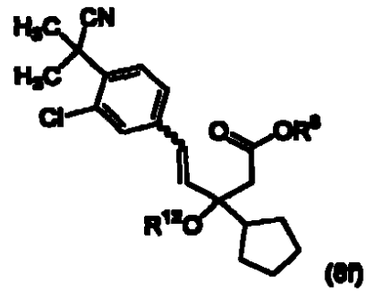
R^{12} es hidrógeno o -C(O)R^{13}; y

R^{13} es alquilo C_1-C_6 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$;

o una sal de los mismos.

En un aspecto adicional, se proporcionan compuestos de fórmula (8e),o una sal de los mismos, en la que R^{12} es hidrógeno.

En otro aspecto adicional más se proporcionan compuestos de fórmula (8f),



(6f)

en la que:

R^8 es hidrógeno o alquilo C_1-C_6;

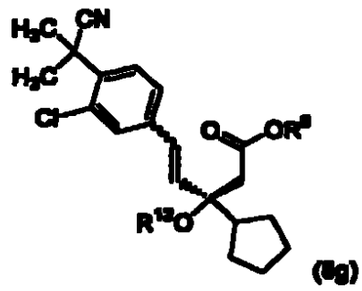
R^{12} es hidrógeno o -C(O)R^{13}; y

R^{13} es alquilo C_1-C_6 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$;

o una sal de los mismos.

Adicionalmente se proporcionan compuestos de fórmula (6f), o una sal de los mismos, en la que R^{12} es hidrógeno.

En otro aspecto adicional más se proporcionan compuestos de fórmula (6g),



(6g)

en la que:

R^8 es hidrógeno o alquilo C_1-C_6;

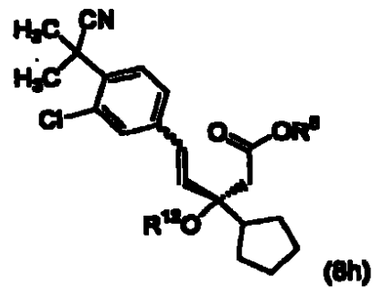
R^{12} es hidrógeno o -C(O)R^{13}; y

R^{13} es alquilo C_1-C_6 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$;

o una sal de los mismos.

Adicionalmente se proporcionan compuestos de fórmula (8g), o una sal de los mismos, en la que R^{12} es hidrógeno.

En otro aspecto adicional de la presente invención se proporcionan compuestos de fórmula (8h),



(8h)

en la que:

R^6 es hidrógeno o alquilo C_1-C_6;

R^{12} es hidrógeno o $-C(O)R^{13}$; y

R^{13} es alquilo C_1-C_6 o $-(CH_2)$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, $-OCH_3$ y $-N$(alquilo C_1-C_6)$_2$;

o una sal de los mismos.

En otro aspecto adicional más se proporcionan compuestos de fórmula (8h), o una sal de los mismos, en la que R^{12} es hidrógeno.

La presente invención también proporciona compuestos de acuerdo con una cualquiera de las fórmulas (8), (8a), (8b), (8c), (8d), (8e), (8f), (8g) y (8h), en las que R^6 es hidrógeno, o cualquiera de estos compuestos en los que R^6 es alquilo C_1-C_6.

En este documento además se proporcionan compuestos de fórmula (8), (8a), o (8b), en la que

R^2 es $-(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), opcionalmente sustituido con al menos un grupo R^4; cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R_7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y

alquinilo C_2-C_8, donde dichos grupos alquilo C_1-C_8, alquenilo C_2-C_8 y alquinilo C_2-C_8 están opcionalmente sustituidos con al menos un R^5;

R^5 es oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN y heterociclilo de 4 a 10 miembros sustituido con R^6;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_8;

R^8 es hidrógeno o alquilo C_1-C_8; y

n es 0, 1, 2, 3, 4, ó 5.

En este documento además se proporcionan compuestos de fórmula (8), (8a), o (8b), en la que

R^2 es -(heterociclilo de 5 a 6 miembros), opcionalmente sustituido con al menos un grupo R^4;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_8, alquenilo C_2-C_8 y alquinilo C_2-C_8, donde dichos grupos alquilo C_1-C_8, alquenilo C_2-C_8 y alquinilo C_2-C_8 están opcionalmente sustituidos con al menos un R^5;

R^5 es oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN y heterociclilo de 4 a 10 miembros sustituido con R^6,

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_8; y

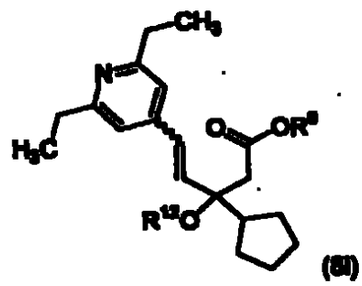
R^8 es hidrógeno o alquilo C_1-C_8;

En este documento además se proporcionan compuestos de fórmula (8), (8a), o (8b), en la que

R^2 es -(4-piridilo), sustituido con al menos un alquilo C_1-C_8; y

R^8 es hidrógeno o alquilo C_1-C_8;

En este documento además se proporcionan compuestos de fórmula (8i),



(8i)

en la que:

R^8 es hidrógeno o alquilo C_1-C_6;

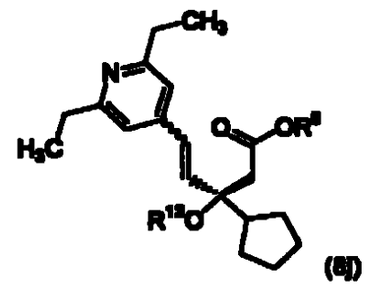
R^{12} es hidrógeno o -C(O)R^{13}; y

R^{13} es alquilo C_1-C_6 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$;

o una sal de los mismos.

En este documento además se proporcionan compuestos de fórmula (8i), o una sal de los mismos, en los que R^{12} es hidrógeno.

En otro aspecto adicional más de la presente invención se proporcionan compuestos de fórmula (8j),



(8j)

en la que:

R^8 es hidrógeno o alquilo C_1-C_6;

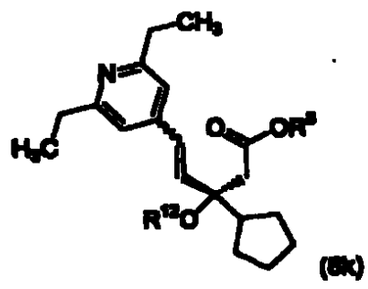
R^{12} es hidrógeno o -C(O)R^{13}; y

R^{13} es alquilo C_1-C_6 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$;

o una sal de los mismos.

En este documento además se proporcionan compuestos de fórmula (8j), o una sal de los mismos, en la que R^{12} es hidrógeno.

Otro aspecto de la presente invención proporciona compuestos de fórmula (8k),



(8k)

en la que:

R^8 es hidrógeno o alquilo C_1-C_6;

R^{12} es hidrógeno o $-C(O)R^{13}$; y

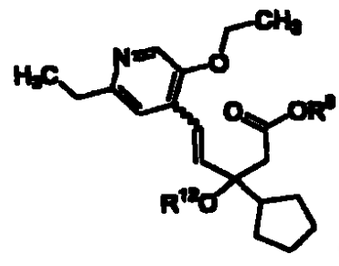
R^{13} es alquilo C_1-C_6 o $-(CH_2)$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, $-OH$, $-OCH_3$ y $-N$(alquilo C_1-C_6)$_2$;

o una sal de los mismos.

Además, en este documento se proporcionan compuestos de fórmula (8k), o una sal de los mismos, en la que R^{12} es hidrógeno.

En este documento, además se proporcionan compuestos de acuerdo una cualquiera de las fórmulas (8l), (8j), o (8k), donde R^8 es hidrógeno, o donde R^8 es alquilo C_1-C_6.

La presente invención además proporciona compuestos de fórmula (8l),



(8l),

en la que:

R^8 es hidrógeno o alquilo C_1-C_6;

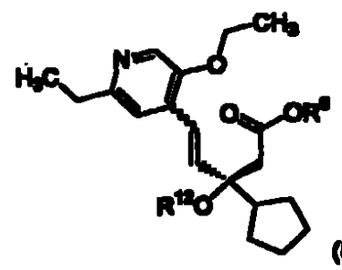
R^{12} es hidrógeno o -C(O)R^{13}; y

R^{13} es alquilo C_1-C_6 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$;

o una sal de los mismos.

Además, en este documento se proporcionan compuestos de fórmula (8l), o una sal de los mismos, en la que R^{12} es hidrógeno.

En otro aspecto adicional más de la presente invención se proporcionan compuestos de fórmula (8m),



(8m),

en la que:

R^8 es hidrógeno o alquilo C_1-C_6;

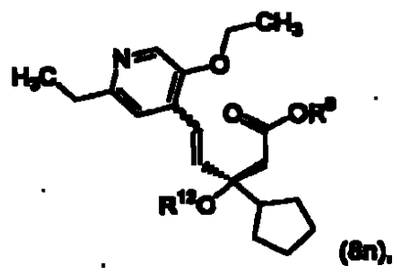
R^{12} es hidrógeno o -C(O)R^{13}; y

R^{13} es alquilo C_1-C_6 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$;

o una sal de los mismos.

En este documento además se proporcionan compuestos de fórmula (8m), o una sal de los mismos, en la que R^{12} es hidrógeno.

La presente invención además proporciona compuestos de fórmula (8n),



(8n),

en la que:

R^8 es hidrógeno o alquilo C_1-C_6;

R^{12} es hidrógeno o -C(O)R^{13}; y

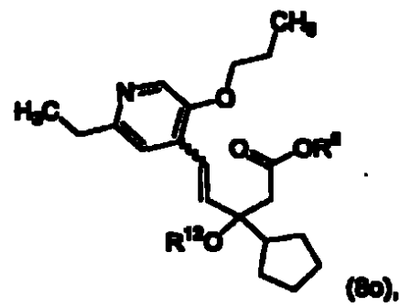
R^{13} es alquilo C_1-C_6 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$;

o una sal de los mismos.

En este documento además se proporcionan compuestos de fórmula (8n), o una sal de los mismos, en la que R^{12} es hidrógeno.

Además, en este documento se proporcionan compuestos de acuerdo con una cualquiera de las fórmulas (8l), (8m), o (8n), en las que R^8 es hidrógeno, o en las que R^8 es alquilo C_1-C_6.

Además, la presente invención proporciona compuestos de fórmula (8o),



(8o),

en la que:

R^8 es hidrógeno o alquilo C_1-C_6;

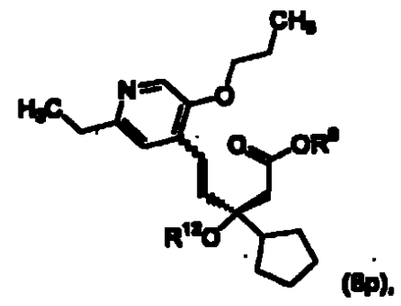
R^{12} es hidrógeno o -C(O)R^{13}; y

R^{13} es alquilo C_1-C_6 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$;

o una sal de los mismos.

Además, en este documento se proporcionan compuestos de fórmula (8o), o una sal de los mismos, en la que R^{12} es hidrógeno.

Además, en este documento se proporcionan compuestos de fórmula (8p),



(8p),

en la que:

R^8 es hidrógeno o alquilo C_1-C_6;

R^{12} es hidrógeno o -C(O)R^{13}; y

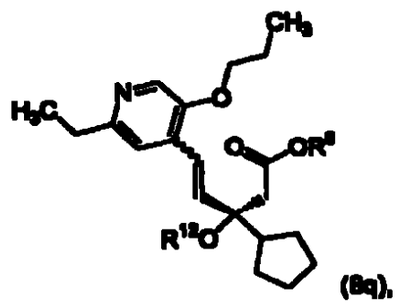
R^{13} es alquilo C_1-C_6 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$;

o una sal de los mismos.

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381

Además, en este documento se proporcionan compuestos de fórmula (8p), o una sal de los mismos, en la que R^{12} es hidrógeno.

Además, en este documento se proporcionan compuestos de fórmula (8q),



(8q),

en la que:

R^8 es hidrógeno o alquilo C_1-C_8;

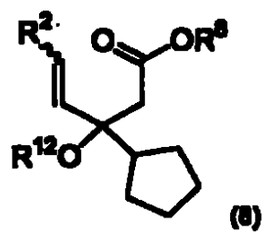
R^{12} es hidrógeno o -C(O)R^{13}; y

R^{13} es alquilo C_1-C_8 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_8, -OH, -OCH_3 y -N(alquilo C_1-C_8)$_2$;

o una sal de los mismos.

Además, en este documento se proporcionan compuestos de fórmula (8q), o una sal de los mismos, en la que R^{12} es hidrógeno.

La presente invención además proporciona métodos para preparar compuestos de fórmula (8),



(8)

en la que:

R^2 es $-(CR^6R^7)_n$arilo C_6-C_{10} o $-(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo arilo C_6-C_{10} o heterociclilo de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, $-CN$, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

R^5 es oxo. cicloalquilo C_3-C_8, arilo C_6-C_{10}, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN y heterociclilo de 4 a 10 miembros sustituido con R^6;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

R^9 es hidrógeno o alquilo C_1-C_6;

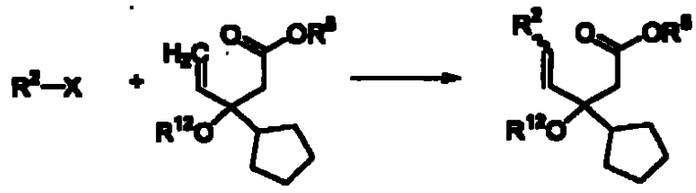
R^{12} es hidrógeno o $-C(O)R^{13}$;

R^{13} es alquilo C_1-C_8 o $-(CH_2)$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, $-OCH_3$ y $-N$(alquilo C_1-$C_6)_2$; y

n es 0, 1, 2, 3, 4, o 5;

comprendiendo dicho método:

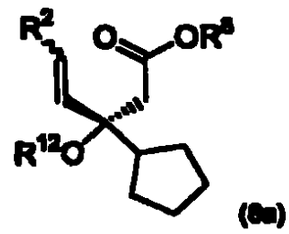
a) tratar un compuesto de fórmula (6), en la que R^2 es como se ha definido anteriormente y X es halógeno o $-OSO_2CF_3$, con un compuesto de fórmula (7) en presencia de un catalizador, donde R^9 es como se ha definido anteriormente en este documento,



(6) (7) (8)

para producir el compuesto de fórmula (8).

Además, en este documento se proporcionan métodos para producir los compuestos de fórmula (8a),



(6a)

en la que:

R^2 es $-(CR^6R^7)_n$arilo C_6-C_{10} o $-(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo arilo C_6-C_{10} o heterociclilo de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, $-CN$, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

R^5 es oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, $-CN$ y heterociclilo de 4 a 10 miembros sustituido con R^6;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

R^8 es hidrógeno o alquilo C_1-C_6;

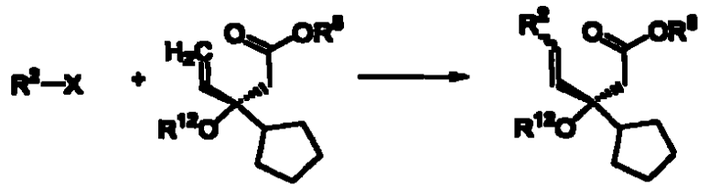
R^{12} es hidrógeno o $-C(O)R^{13}$;

R^{13} es alquilo C_1-C_6 o $-(CH_2)$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, $-OH$, $-OCH_3$ y $-N$(alquilo C_1-C_6)$_2$; y

n es 0, 1, 2, 3, 4, o 5;

comprendiendo dicho método:

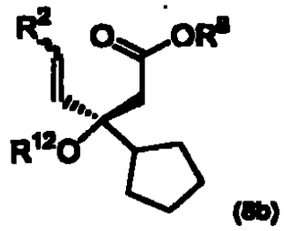
a) tratar un compuesto de fórmula (6), en la que R^2 es como se ha definido anteriormente y X es halógeno, $-OSO_2CF_3$, con un compuesto de fórmula (7a) en presencia de un catalizador, donde R^8 es como se ha definido anteriormente en este documento,



(6) (7a) (8a)

para producir el compuesto de fórmula (8a).

La presente invención además proporciona métodos para preparar compuestos de fórmula (8b),



(8b)

en la que:

R^2 es $-(CR^6R^7)_n$arilo C_6-C_{10} o $-(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo arilo C_6-C_{10} o heterociclilo de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, NR^6R^7, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

R^5 es oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN y heterociclilo de 4 a 10 miembros sustituido con R^6,

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

R^8 es hidrógeno o alquilo C_1-C_6;

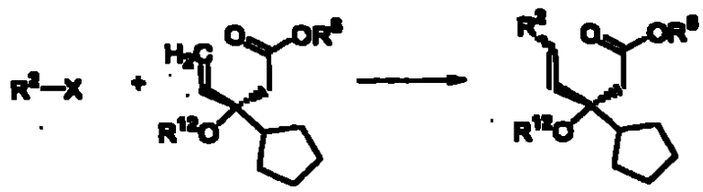
R^{12} es hidrógeno o $-C(O)R^{13}$;

R^{13} es alquilo C_1-C_6 o $-(CH_2)$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, $-OCH_3$ y $-N$(alquilo C_1-C_6)$_2$; y

n es 0, 1, 2, 3, 4, o 5;

comprendiendo dicho método:

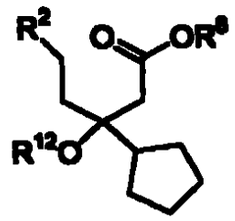
a) tratar un compuesto de fórmula (6), en la que R^2 es como se ha definido anteriormente y X es halógeno o $-OSO_2CF_3$, con un compuesto de fórmula (7b) en presencia de un catalizador, donde R^8 es como se ha definido anteriormente,



(6) (7b) (8b)

para producir el compuesto de fórmula (8a).

Además, en este documento se proporcionan métodos para preparar un compuesto de fórmula (9),



(9)

en la que:

R^2 es $-(CR^6R^7)_n$arilo C_6-C_{10} o $-(CR^6R^7)_n$(heterocicilo de 5 a 6 miembros), donde dicho grupo arilo C_6-C_{10} o heterocicilo de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

R^5 es oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN y hete-

rociclilo de 4 a 10 miembros sustituido con R^8;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

R^8 es hidrógeno o alquilo C_1-C_6;

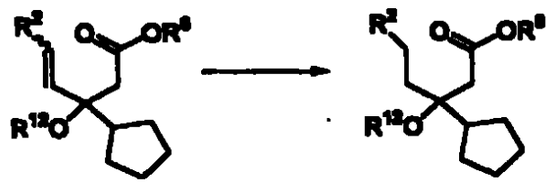
R^{12} es hidrógeno o -C(O)R^{13};

R^{13} es alquilo C_1-C_8 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$; y

n es 0, 1, 2, 3, 4, o 5;

comprendiendo dicho método:

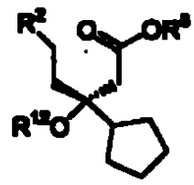
a) tratar un compuesto de fórmula (8), en la que R^2 y R^8 son como se han definido en este documento, con un agente reductor en presencia de un catalizador,



(8) (9)

para producir el compuesto de fórmula (9).

Además, en este documento se proporcionan métodos para preparar compuestos de fórmula (9a),



(9a)

en la que:

R^2 es -(CR^6R^7)$_n$arilo C_6-C_{10} o -(CR^6R^7)$_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo arilo C_6-C_{10} o heterociclilo de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

cada R^4 se selecciona independientemente entre halo, -OR^8, oxo, -NR^6R^7, -CF_3,

-CN, -C(O)R^6, -C(O)OR^6, -OC(O)R^6, -NR^6C(O)R^7, -NR^6C(O)OR^7, -NR^6C(O)N$R^5$$R^7$, -C(O)N$R^6$$R^7$, -$SO_2NR^6$$R^7$, -N$R^6$$SO_2$$R^7$, alquilo C_1-C_8, alquenilo C_2-C_8 y alquinilo C_2-C_8, donde dichos grupos alquilo C_1-C_8, alquenilo C_2-C_8 y alquinilo C_2-C_8 están opcionalmente sustituidos con al menos un R^5;

R^5 es oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, -OR^6, -C(O)OR^6, -N$R^6$$R^7$, -CN y heterociclilo de 4 a 10 miembros sustituido con R^6;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_8;

R^8 es hidrógeno o alquilo C_1-C_8;

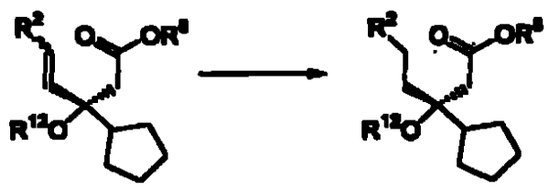
R^{12} es hidrógeno o-C(O)R^{13};

R^{13} es alquilo C_1-C_8 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_8, -OH, -OCH_3 y -N(alquilo C_1-C_8)$_2$; y

n es 0, 1, 2, 3, 4, o 5;

comprendiendo dicho método:

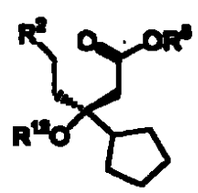
a) tratar un compuesto de fórmula (8a), en la que R^2 y R^8 son como se han definido en este documento, con un agente reductor en presencia de un catalizador,



(8a) (9a)

para producir el compuesto de fórmula (9a).

Además, en este documento se proporcionan métodos para preparar compuestos de fórmula (9b),



(9b)

390
388

en la que:

R^2 es $-(CR^6R^7)_n$arilo C_6-C_{10} o $-(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo arilo C_6-C_{10} o heterociclilo de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, $-CN$, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde cada uno de dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 está opcionalmente sustituido con al menos un R^5;

R^5 es oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, $-CN$ y heterociclilo de 4 a 10 miembros sustituido con R^6,

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

R^8 es hidrógeno o alquilo C_1-C_6;

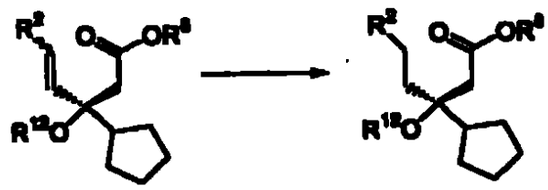
R^{12} es hidrógeno o $-C(O)R^{13}$;

R^{13} es alquilo C_1-C_6 o $-(CH_2)$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, $-OH$, $-OCH_3$ y $-N$(alquilo C_1-C_6)$_2$; y

n es 0, 1, 2, 3, 4, o 5;

comprendiendo dicho método:

a) tratar un compuesto de fórmula (8b), en la que R^2 y R^8 con como se han definido en este documento, con un agente reductor en presencia de un catalizador,

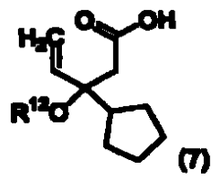


(8b) (9b)

para producir el compuesto de fórmula (9b).

Además, se proporcionan métodos donde dicho catalizador se selecciona entre paladio y platino y métodos donde dicho agente reductor es hidrógeno. Además se proporcionan métodos donde dicho agente reductor es hidrógeno y dicho catalizador se selecciona entre paladio y platino.

Además, en este documento se proporcionan métodos para preparar compuestos enriquecidos estereoisoméricamente de fórmula (7),



(7)

en la que:

R^{12} es hidrógeno o $-C(O)R^{13}$; y

R^{13} es alquilo C_1-C_6 o $-(CH_2)$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, $-OCH_3$ y $-N$(alquilo C_1-C_6)$_2$;

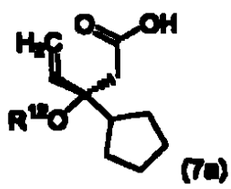
comprendiendo dicho método:

a) tratar un compuesto de fórmula (7) con una base quiral, no racémica, para producir una mezcla de sales diastereoméricas;

b) separar dichas sales diastereoméricas entre sí para producir una sal diastereomérica enriquecida estereoisoméricamente; y

c) convertir dicha sal diastereomérica enriquecida estereoisoméricamente en un compuesto enriquecido estereoisoméricamente de fórmula (7).

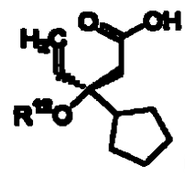
Además, en este documento se proporcionan métodos en los que el compuesto enriquecido estereoisoméricamente de fórmula (7) es (7a),



(7a)

o es un compuesto de fórmula (7b),

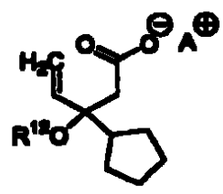
392
390



(7b).

En otro aspecto adicional más se proporcionan los métodos descritos anteriormente; en los que dicha base quiral no racémica es una amina quiral no racémica. Además, se proporcionan métodos en los que dicha amina quiral no racémica se selecciona entre un enantiómero de 1,2,3,4-tetrahidro-1-naftilamina, 1,2,3,4-tetrahidro-1-naftilamina, 1-(2-naftil)etilamina, 1-(2-naftil)etilamina y norefedrina. Además, se proporcionan métodos en los que la amina quiral no racémica es (S)-1,2,3,4tetrahidro-1-naftilamina.

Además, en este documento se proporcionan compuestos de fórmula (7c),



(7c)

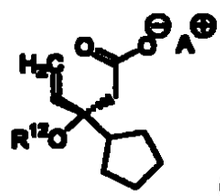
en la que:

R^{12} es hidrógeno o-C(O)R^{13};

R^{13} es alquilo C_1-C_8 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$; y

A es un contraión adecuado.

En un aspecto adicional de la presente invención se proporcionan compuestos de fórmula (7d),



(7d)

393
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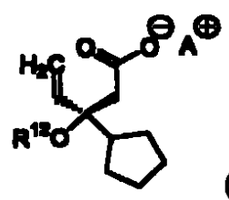
en la que:

R^{12} es hidrógeno o -C(O)R^{13};

R^{13} es alquilo C_1-C_8 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_8, -OH, -OCH_3 y -N(alquilo C_1-C_8)$_2$; y

A es un contraión adecuado.

Además, en este documento se proporcionan compuestos de fórmula (7e),



(7e)

en la que:

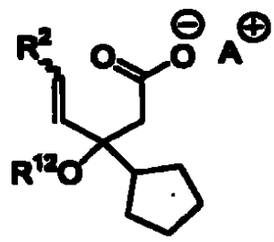
R^{12} es hidrógeno o-C(O)R^{13};

R^{13} es alquilo C_1-C_8 o -(CH_2)(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_8, -OH, -OCH_3 y -N(alquilo C_1-C_8)$_2$; y

A es un contraión adecuado.

En otro aspecto más de la presente invención se proporcionan compuestos de fórmulas (7c), (7d) y (7e), en las que dicho contraión se obtiene a partir de una amina. Además, se proporcionan compuestos en los que dicha amina es una amina quiral no racémica. Además, se proporcionan compuestos en los que dicha amina quiral no racémica se selecciona entre un enantiómero de 1,2,3,4-tetrahidro-1naftilamina, 1,2,3,4-tetrahidro-1-naftilamina, 1-(2-naftil)etilamina, norefedrina, norefedrina. Además, se proporcionan métodos en los que la amina quiral no racémica es (S)-1,2,3,4tetrahidro-1-naftilamina.

Además, en este documento se proporcionan compuestos de fórmula (8c)



(8c)

en la que:

R^2 es $-(CR^6R^7)_n$arilo C_6-C_{10} o $-(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo arilo C_6-C_{10} o heterociclilo de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(=NR^6)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde cada uno de dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 está opcionalmente sustituido con al menos un R^5;

R^5 es oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, $-OR^6$, $-C(O)OR_6$, $-NR^6R^7$, -CN y heterociclilo de 4 a 10 miembros sustituido con R^6,

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

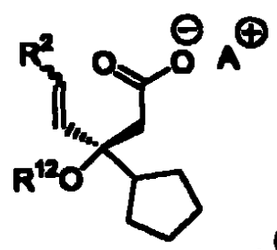
R^{12} es hidrógeno o $-C(O)R^{13}$;

R^{13} es alquilo C_1-C_6 o $-(CH_2)$(arilo C_6-C_{10}), donde dicho grupo arilo está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, $-OCH_3$ y $-N$(alquilo C_1-C_6)$_2$;

n es 0, 1, 2, 3, 4, ó 5; y

A es un contraión adecuado.

La presente invención además proporciona compuestos de fórmula (8d)



(8d)

en la que:

R^2 es $-(CR^6R^7)_n$arilo C_6-C_{10} o $-(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo arilo C_6-C_{10} o heterociclilo de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

cada R^4 se selecciona independientemente entre halo, $-OR^0$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$, $-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

R^5 es oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN y heterociclilo de 4 a 10 miembros sustituido con R^6;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

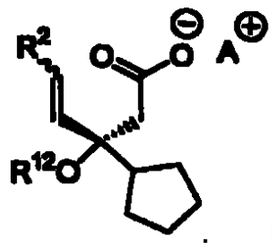
R^{12} es hidrógeno o $-C(O)R^{13}$;

R^{13} es alquilo C_1-C_6 o $-(CH_2)$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, $-OCH_3$ y $-N$(alquilo C_1-C_6)$_2$;

n es 0, 1, 2, 3, 4, ó 5; y

A es un contralón adecuado.

Además, en este documento se proporcionan compuestos de fórmula (8e)



(8e)

en la que:

R^2 es $-(CR^6R^7)_n$arilo C_6-C_{10} o $-(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo arilo C_6-C_{10} o heterociclilo de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

cada R^4 se selecciona independientemente entre halo, $-OR^6$, oxo, $-NR^6R^7$, $-CF_3$, -CN, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^7$, $-NR^6C(O)NR^6R^7$,

$-C(O)NR^6R^7$, $-SO_2NR^6R^7$, $-NR^6SO_2R^7$, alquilo C_1-C_8, alquenilo C_2-C_8 y alquinilo C_2-C_8, donde dichos grupos alquilo C_1-C_8, alquenilo C_2-C_8 y alquinilo C_2-C_8 están opcionalmente sustituidos con al menos un R^6;

R^6 es oxo, cicloalquilo C_3-C_8, arilo C_6-C_{10}, $-OR^6$, $-C(O)OR^6$, $-NR^6R^7$, -CN y heterociclilo de 4 a 10 miembros sustituido con R^6,

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_8;

R^{12} es hidrógeno o $-C(O)R^{13}$;

R^{13} es alquilo C_1-C_8 o $-(CH_2)$(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_8, -OH, $-OCH_3$ y -N(alquilo C_1-C_8)$_2$;

n es 0, 1, 2, 3, 4, ó 5; y

A es un contraión adecuado.

Además, en este documento se proporcionan compuestos de fórmulas (8c), (8d) y (8e), en las que dicho contralón adecuado se obtiene a partir de una amina. Además, se proporciona cualquiera de estos compuestos en los que la amina es una amina quiral no racémica. Además, se proporciona cualquiera de estos compuestos en los que la amina quiral no racémica se selecciona entre un enantiómero de 1,2,3,4-tetrahidro-1-naftilamina, 1-(2-naftil)etilamina y norefedrina.

Tal y como se emplea en este documento, los términos que comprende y que incluye se emplean en su sentido amplio, no limitativo.

El término "alquilo C_1-C_8", como se usa en este documento, a menos que se indique otra cosa, incluye radicales hidrocarbonados monovalentes saturados que tienen restos lineales, ramificados o cíclicos (incluyendo restos bicíclicos condensados y enlazados y espirocíclicos), o una combinación de los restos anteriores, que contienen de 1 a 6 átomos de carbono. Para que un grupo alquilo tenga restos cíclicos, el grupo tiene que tener al menos tres átomos de carbono.

Un alquilo inferior significa un grupo alquilo que tiene de 1 a 4 átomos de carbono en su cadena. El término "heteroalquilo" se refiere a un grupo alquilo de cadena lineal o ramificada, que tiene de 2 a 12 átomos en la cadena, uno o más de los cuales es un heteroátomo seleccionado de S, O y N. Heteroalquilos a modo de ejemplo incluyen éteres de alquilo, aminas secundarias y terciarias, sulfuros de alquilo y similares.

El término "alquenilo C_2-C_8", como se usa en este documento, a menos que se indique otra cosa, incluye restos alquilo que tienen al menos un doble enlace carbono-

carbono en el que alquilo es como se ha definido anteriormente e incluye isómeros E y Z de dicho resto alquenilo y que tienen de 2 a 6 átomos de carbono.

El término "alquinilo C_2-C_6", como se usa en este documento, a menos que se indique otra cosa, incluye restos alquilo que tienen al menos un triple enlace carbono-carbono donde el alquilo es como se ha definido anteriormente y que contienen de 2 a 6 átomos de carbono.

El término carbociclo se refiere a una estructura de anillo, saturada, parcialmente saturada, insaturada o aromática, monocíclica o policíclica fusionada o no fusionada, que tiene sólo átomos de carbono en el anillo (no tiene heteroátomos, es decir, no tiene átomos de carbono en el anillo). Carbociclos a modo de ejemplo incluyen grupos cicloalquilo, arilo y cicloalquil-arilo.

Un "grupo cicloalquilo C_3-C_{10}" se refiere a una estructura de anillo saturada o parcialmente saturada, monocíclica o condensada o espiro policíclica que tiene un total de 3 a 10 átomos de carbono en el anillo (pero no heteroátomos). Cicloalquilos a modo de ejemplo incluyen grupos ciclopropilo, ciclobutilo, ciclopentilo, ciclopentenilo, ciclohexilo, cicloheptilo, adamantilo y grupos similares.

Un "grupo heterocicloalquilo" se refiere a una estructura de anillo monocíclico o condensado o espiro policíclico que está saturado o parcialmente saturado y que tiene un total de 3 a 18 átomos por anillo, incluyendo de 1 a 5 heteroátomos seleccionados entre nitrógeno, oxígeno y azufre. Los ejemplos ilustrativos de grupos heterocicloalquilo incluyen pirrolidinilo, tetrahidrofurilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, aziridinilo y grupos similares.

El término "arilo C_6-C_{10}", como se usa en este documento, a menos que se indique otra cosa, incluye un resto orgánico derivado de un hidrocarburo aromático por la retirada de un hidrógeno, tal como fenilo o naftilo. El término "fenilo" y el símbolo "Ph," como se usa en este documento, se refieren a un grupo C_6H_5.

El término "heterociclilo de 4 a 10 miembros", como se usa en este documento, a menos que se indique otra cosa, incluye grupos heterocíclicos aromáticos y no aromáticos que contienen de uno a cuatro heteroátomos seleccionados entre O, S y N, donde cada grupo heterocíclico tiene de 4 a 10 átomos en su sistema de anillo y con la condición de que el anillo de dicho grupo no contenga dos átomos adyacentes de O o S. Además, los átomos de azufre contenidos en tales grupos heterocíclicos pueden oxidarse con uno o dos átomos de azufre. Los grupos heterocíclicos no aromáticos incluyen grupos que tienen sólo 4 átomos en su sistema de anillo, pero los grupos heterocíclicos aromáticos tienen que tener al menos 5 átomos en su sistema de anillo. Los

grupos heterocíclicos incluyen sistemas anulares benzo-fusionados. Un ejemplo de un grupo heterocíclico de 4 miembros es azetidinilo (obtenido a partir de azetidina). Un ejemplo de un grupo heterocíclico de 5 miembros es tiazolilo y un ejemplo de un grupo heterocíclico de 10 miembros es quinolinilo. Son ejemplos de grupos heterocíclicos no aromáticos pirrolidinilo, tetrahidrofuranilo, dihidrofuranilo, tetrahidrotienilo, tetrahidropiranilo, dihidropiranilo, tetrahidrotiopiranilo, piperidino, morfolino, tiomorfolino, tioxanilo, piperazinilo, azetidinilo, oxetanilo, tietanilo, homopiperidinilo, oxepanilo, tiepanilo, oxazepinilo, diazepinilo, tiazepinilo, 1,2,3,6tetrahidropiridinilo, 2-pirrolinilo, 3-pirrolinilo, indolinilo, 2H-piranilo, 4H-piranilo, dioxanilo, 1,3dioxolanilo, pirazolinilo, ditianilo, ditiolanilo, dihidropiranilo, dihidrotienilo, dihidrofuranilo, pirazolidinilo, imidazolinilo, imidazolidinilo, 3-azabiciclo[3.1.0]hexanilo, 3-azabiciclo[4.1.0]heptanilo, 3Hindolilo y quinolizinilo. Son ejemplos de grupos heterocíclicos aromáticos piridinilo, imidazolilo, pirimidinilo, pirazolilo, triazolilo, pirazinilo, tetrazolilo, furilo, tienilo, isoxazolilo, tiazolilo, oxazolilo, isotiazolilo, pirrolilo, quinolinilo, isoquinolinilo, indolilo, bencimidazolilo, benzofuranilo, cinnolinilo, indazolilo, indolizinilo, ftalazinilo, piridazinilo, triazinilo, isoindolilo, pteridinilo, purinilo, oxadiazolilo, tiadiazolilo, furazanilo, benzofurazanilo, benzotiofenilo, benzotiazolilo, benzoxazolilo, quinazolinilo, quinoxalinilo, naftiridinilo y furopiridinilo. Los grupos anteriores, al obtenerse a partir de los grupos enumerados anteriormente, pueden estar fijados a C o fijados a N, cuando sea posible. Por ejemplo, un grupo obtenido a partir de pirrol puede ser pirrol-1-ilo (fijado a N) o pirrol-3-ilo (fijado a C). Además, un grupo obtenido a partir de imidazol puede ser imidazol-1-ilo (fijado a N) o imidazol-3-ilo (fijado a C). Un ejemplo de un grupo heterocíclico en el que 2 átomos de carbono del anillo están sustituidos con restos (=O) es 1,1-dioxotiomorfolinilo.

El término "heterociclilo de 5 a 6 miembros" se refiere a grupos heterocíclicos aromáticos y no aromáticos que contienen de uno a cuatro heteroátomos seleccionados cada uno entre O, S y N y donde cada grupo heterocíclico tiene un total de 5 a 6 átomos en su sistema de anillos y con la condición de que el anillo de dicho grupo no contenga dos átomos de O o S adyacentes. Los átomos de azufre contenidos en dichos grupos heterocíclicos pueden oxidarse con uno o dos átomos de azufre. Además, cualquier átomo en el grupo heterociclilo de 5 a 6 miembros puede estar sustituido con un grupo oxo (=O), si tal sustitución da como resultado un compuesto estable. Los ejemplos de grupos heterocíclicos no aromáticos incluyen, pero sin limitación, pirrolidinilo, tetrahidrofuranilo, dihidrofuranilo, tetrahidrotienilo, tetrahidropiranilo, dihidropiranilo, tetrahidrotiopiranilo, piperidino, morfolino, tiomorfolino, tioxanilo, piperazinilo, azetidinilo, oxetanilo, tietanilo, homopiperidinilo, oxepanilo, tiepanilo, oxazepinilo, diazepinilo, tiazepinilo, 1,2,3,6tetrahidropiridinilo, 2-pirrolinilo, 3-pirrolinilo,

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zepinilo, 1,2,3,6tetrahidropiridinilo, 2-pirrolinilo, 3-pirrolinilo, indolinilo, 2H-piranilo, 4H-piranilo, dioxanilo, 1,3dioxolanilo, pirazolinilo, ditianilo, ditiolanilo, dihidropiranilo, dihidrotienilo, dihidrofuranilo, pirazolidinilo, imidazolinilo, imidazolidinilo, 3-azabiciclo[3.1.0]hexanilo, 3-azabiciclo[4.1.0]heptanilo, 3Hindolilo y quinolizinilo. Los ejemplos de grupos heterocíclicos aromáticos incluyen, pero sin limitación, piridinilo, imidazolilo, pirimidinilo, pirazolilo, triazolilo, pirazinilo, tetrazolilo, furilo, tienilo, isoxazolilo, tiazolilo, oxazolilo, isotiazolilo, pirrolilo, quinolinilo, isoquinolinilo, indolilo, benzimidazolilo, benzofuranilo, cinnolinilo, indazolilo, indolizinilo, ftalazinilo, piridazinilo, triazinilo, isoindolilo, pteridinilo, purinilo, oxadiazolilo, tiadiazolilo, furazanilo, quinazolinilo y quinoxalinilo. Los grupos anteriores, al obtenerse a partir de los grupos enumerados anteriormente, pueden estar fijados a C o fijados a N, cuando sea posible. Por ejemplo, un grupo derivado del pirrol puede ser pirrol-1-ilo (unido al N) o pirrol-3-ilo (unido al C). Además, un grupo derivado de imidazol puede ser imidazol-1-ilo (unido a N) o imidazol-3-ilo (unido a C). Un ejemplo de un grupo heterocíclico en el que 2 átomos de carbono del anillo están sustituidos con restos oxo (=0) es 1,1-dioxotiomorfolinilo.

Un "grupo heteroarilo" significa una estructura en anillo aromática, monocíclica o policíclica fusionada o espiro que tiene de 4 a 18 átomos en el anillo, que incluyen desde 1 a 5 heteroátomos seleccionados entre nitrógeno, oxígeno y azufre. Ejemplos ilustrativos de grupos heteroarilos incluyen pirrolilo, tienilo, oxazolilo, pirazolilo, tiazolilo, furilo, piridinilo, pirazinilo, triazolilo, tetrazolilo, indolilo, quinolinilo, quinoxalinilo, benzotiazolilo, benzodioxinilo, benzodioxolilo, benzooxazolilo y similares.

El término "alcoxi", como se usa en este documento, a menos que se indique otra cosa, incluye grupos O-alquilo, donde alquilo es como se ha definido anteriormente.

El término "amino" significa el resto $-NH_2$.

Los términos "halógeno" y "halo," como se usan en este documento representan flúor, cloro, bromo o yodo.

El término "oxo," como se usa en este documento, se refiere a un grupo (=O). Dicho grupo puede estar unido a un átomo de carbono o a un heteroátomo en los compuestos de la presente invención, si dicha sustitución da como resultado un compuesto estable.

El término "trifluorometilo," como se usa en este documento, se entiende que representa un grupo $-CF_3$.

El término "trifluorometoxi," como se usa en este documento, se entiende que se refiere a un grupo $-OCF_3$.

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El término "ciano," como se usa en este documento, se entiende que representa un grupo -CN.

El término "sustituido" se refiere a que el grupo o el resto especificado soporta uno o más sustituyentes. El término "no sustituido" se refiere a que el grupo especificado no soporta sustituyentes. El término "opcionalmente sustituido" se refiere a que el grupo especificado está sin sustituir o sustituido con uno o más sustituyentes.

El término "HCV," como se usa en este documento, se refiere al virus de la Hepatitis C.

Las expresiones "inhibición del virus de la Hepatitis C" e "inhibición de la replicación del virus de la Hepatitis C" significa la inhibición de la replicación del virus de la Hepatitis C *in vitro* o *in vivo*, tal como en un mamífero, tal como un ser humano, poniendo en contacto el virus de la Hepatitis C con una cantidad inhibidora de la replicación de HCV de un compuesto de la presente invención o una sal farmacéuticamente aceptable o solvato del mismo. Tal inhibición puede tener lugar *in vivo*, tal como en un mamífero, tal como un ser humano, por medio de la administración al mamífero de una cantidad para inhibir el virus de la Hepatitis C de un compuesto de la presente invención. La cantidad de un compuesto de la presente invención necesaria para inhibir la replicación del virus HCV *in vitro* o *in vivo*, tal como en un mamífero, tal como un ser humano, puede determinarse usando métodos conocidos por los especialistas habituales en la técnica. Por ejemplo, se puede administrar a un mamífero una cantidad de un compuesto de la invención, o bien sólo o como parte de una formulación farmacéuticamente aceptable. Después pueden extraerse muestras de sangre del mamífero y la cantidad de virus de la Hepatitis C en la muestra puede cuantificarse usando métodos conocidos por los especialistas habituales en la técnica. Una reducción de la cantidad de virus de la Hepatitis C en la muestra en comparación con la cantidad encontrada en la sangre antes de la administración de un compuesto de la invención representaría la inhibición de la replicación del virus de la Hepatitis C en el mamífero. La administración de un compuesto de la invención al mamífero puede estar en forma de una sola dosis o una serie de dosis en días sucesivos.

Un "agente inhibidor de HCV" significa un compuesto de la presente invención o una sal farmacéuticamente aceptable o solvato del mismo.

La expresión "cantidad inhibidora de HCV," como se usa en este documento, se refiere a una cantidad de un compuesto de la presente invención que es suficiente para inhibir la replicación del virus de la Hepatitis C cuando se administra a un mamífero, tal como un ser humano.

La expresión "cantidad inhibidora de la polimerasa de HCV", como se usa en este documento, significa una cantidad de un compuesto de la presente invención que es suficiente para inhibir la función de la enzima polimerasa del virus Hepatitis C cuando el compuesto se pone en contacto con la enzima.

Se desea que un "solvato" quiera decir una forma de solvato farmacéuticamente aceptable de un compuesto específico que retenga la eficacia biológica de tal compuesto. Los ejemplos de solvatos incluyen compuestos de la invención en combinación con disolventes tales como, pero sin limitación, agua, isopropanol, etanol, metanol, DMSO, acetato de etilo, ácido acético o etanolamina. Una "sal farmacéuticamente aceptable" se entiende que se refiere a una sal que conserva la eficacia biológica de los ácidos y bases libres del derivado especificado y que no es biológicamente ni de otra forma indeseable. Los ejemplos de sales farmacéuticamente aceptables incluyen sulfatos, pirosulfatos, bisulfatos, sulfitos, bisulfitos, fosfatos, monohidrogenfosfatos, dihidrogenfosfatos, metafosfatos, pirofosfatos, cloruros, bromuros yoduros, acetatos, propionatos, decanoatos, caprilatos, acrilatos, formiatos, isobutiratos, caproatos, heptanoatos, propiolatos, oxalatos, malonatos, succinatos, suberatos, sebacatos, fumaratos, maleatos, butina-1,4-dioatos, hexina-1,6-dioatos, benzoatos, clorobenzoatos, metilbenzoatos, dinitrobenzoatos, hidroxibenzoatos, metoxibenzoatos, ftalatos, sulfonatos, xilenosulfonatos, fenilacetatos, fenilpropionatos, fenilbutiratos, citratos, lactatos, γ-hidroxibutiratos, glicolatos, tartratos, metano-sulfonatos, propanosulfonatos, naftaleno-1-sulfonatos, naftaleno-2-sulfonatos y mandelatos.

El término "tratar", como se emplea en este documento, a no ser que se indique otra cosa, significa invertir, aliviar, inhibir el progreso de, o prevenir el trastorno o estado al que se aplica dicho término, o uno o más síntomas de dicho trastorno o estado. El término "tratamiento", como se emplea en este documento, a no ser que se indique otra cosa, se refiere al acto de tratar tal y como se ha definido "tratar" inmediatamente más arriba.

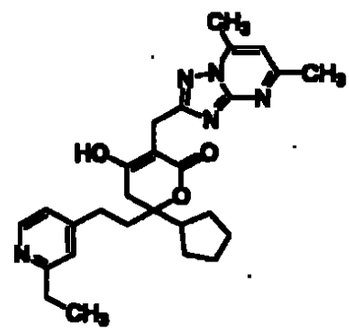
La frase "sal(es) farmacéuticamente aceptable(s)", como se usa en este documento, salvo que se indique lo contrario, incluye sales de grupos ácidos o básicos que pueden estar presentes en los compuestos de la presente invención. Los compuestos de la invención que son básicos en la naturaleza son capaces de formar una amplia diversidad de sales con diversos ácidos inorgánicos y orgánicos. Los ácidos que pueden usarse para preparar sales de adición de ácidos farmacéuticamente aceptables de tales compuestos básicos de la presente invención son aquellos que forman sales de adición de ácidos no tóxicas, es decir, sales que contienen aniones farmacológicamen-

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te aceptables, tales como las sales acetato, bencenosulfonato, benzoato, bicarbonato, bisulfato, bitartrato, borato, bromuro, edetato cálcico, camsilato, carbonato, cloruro, clavulanato, citrato, dihidrocloruro, edetato, edisilato, estolato, esilato, etilsuccinato, fumarato, gluceptato, gluconato, glutamato, glicolilarsanilato, hexilresorcinato, hidrabamina, hidrobromuro, hidrochloruro, yoduro, isotionato, lactato, lactobionato, laurato, malato, maleato, mandelato, mesilato, metilsulfato, mucato, napsilato, nitrato, oleato, oxalato, pamoate (embonato), palmitato, pantotenato, fosfato/difosfato, poligalacturonato, salicilato, estearato, subacetato, succinato, tannato, tartrato, teoclato, tosilato yoduro de trietilo y valerato.

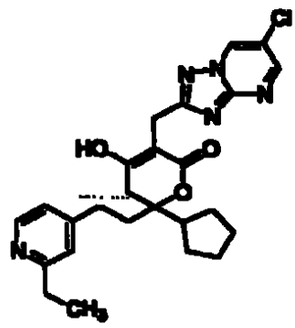
Se entiende que las frases "cantidad terapéuticamente eficaz," "cantidad eficaz" y "cantidad inhibidora de HCV" significan la cantidad de un agente de la invención que, cuando se administra a un mamífero en necesidad de tratamiento, es suficiente para efectuar el tratamiento de lesiones o estados de enfermedad aliviadas por la inhibición de la replicación de ARN de HCV, tal como para la potenciación de terapias contra el cáncer o la inhibición de la neurotoxicidad posterior a apoplejía, traumatismo craneal y enfermedades neurodegenerativas. La cantidad de un agente inhibidor de HCV dado usada en el método de la invención que será terapéuticamente eficaz variará dependiendo de factores tales como el agente inhibidor de HCV particular, el estado de enfermedad y su gravedad, la identidad y características del mamífero que lo necesita, pudiendo determinarse la cantidad de manera rutinaria por los especialistas en la técnica.

El término "6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2-(2etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona," como se usa en este documento, se refiere a un compuesto químico con la estructura:

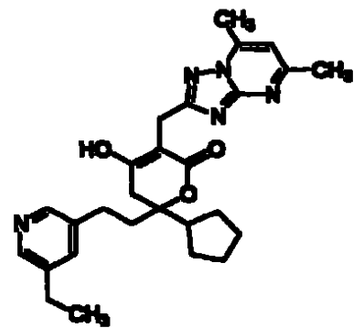


Como se usa en este documento, el término "3-((6-cloro[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6ciclopentil-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,8-dihidro-2H-

piran-2-ona" se refiere a un compuesto químico con la estructura:



El término "6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5etilpiridin-3-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona," como se usa en este documento, se refiere a un compuesto químico con la estructura:



El término "tratamiento", como se usa en este documento, se refiere a un proceso o procesos químicos en los que se deja que dos o más reactivos entren en contacto entre sí para efectuar un cambio o transformación química. Por ejemplo, cuando se deja que entre en contacto el reactivo A y el reactivo B entre sí para producir un nuevo compuesto químico C, se dice que A ha "reaccionado" con B para producir C.

Como se usa en este documento, el término "catalizador" se refiere a un elemento químico o compuesto que aumenta la velocidad de una reacción química reduciendo la energía de activación, pero que se mantiene sin cambiar por la reacción. Los ejemplos de catalizadores incluyen, pero sin limitación, paladio (0) y platino (0). En este documento se contempla específicamente que dicho catalizador puede formarse in situ durante el transcurso de una reacción química, a partir de los denominados "precatalizadores", pero nunca puede observarse realmente o aislarse. Tales precatalizadores son compuestos químicos que son capaces de convertirse in situ durante

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el transcurso de una reacción química en un elemento o compuesto química y catalíticamente competente. Los ejemplos de pre-catalizadores incluyen, pero sin limitación, $PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(OH)_2$, $Pd(PPh_3)_4$, $Pt(OH)_2$ y $PtCl^2$.

La expresión "agente reductor", como se usa en este documento, se refiere a un elemento o compuesto químico que proporciona electrones para otro elemento o compuesto químico en una mezcla de reacción. Como alternativa, se refiere a un elemento o compuesto químico que es capaz de producir un compuesto químico saturado a partir de un compuesto químico insaturado por la adición de hidrógeno. Por ejemplo, la adición de hidrógeno a un alqueno de la presente invención para producir un alqueno saturado se denomina "reducción". UN agente reductor es un elemento o compuesto químico que es capaz de realizar dicha reducción, normalmente en presencia de un catalizador. Los ejemplos de agentes reductores incluyen, pero sin limitación, hidrógeno, ácido fórmico y sales de ácido fórmico, tales como formiato amónico.

El término "proteger,como se usa en este documento, se refiere a un proceso en el que un grupo funcional en un compuesto químico se enmascara selectivamente mediante un grupo funcional no reactivo para permitir que ocurra una reacción o reacciones selectivas en cualquier sitio en dicho compuesto químico. tales grupos funcionales no reactivos se denominan en este documento "grupos protectores." Por ejemplo, el término "grupo protector de hidroxilo," como se usa en este documento se refiere a aquellos grupos que son capaces de enmascarar selectivamente la reactividad de un grupo hidroxilo (-OH). El término grupo protector adecuado,como se usa en este documento se refiere a aquellos grupos protectores que son útiles en la preparación de los compuestos de la presente invención. Dichos grupos generalmente pueden introducirse y retirarse selectivamente usando condiciones de reacción moderadas que no interfieren con otras porciones de los compuestos en cuestión. Los grupos protectores que son adecuados para usar en los procesos y métodos de la presente invención son conocidos para los especialistas en la técnica. Las propiedades químicas de tales grupos protectores, métodos para su introducción y su retirada pueden encontrarse, por ejemplo, en T. Greene y P. Wuts, *Protective Groups In Organic Synthesis* (3rd ed.), John Wiley & Sons, NY (1999). Los términos "desprotección", "desprotegido" o "desproteger", como se usan en este documento, pretenden hacer referencia al proceso de retirar un grupo protector de un compuesto.

Los términos "hidrolizar", "hidrólisis" e "hidrolizado", como se usan en este documento, significan y se refieren a una reacción química en la que un éster, una amida o ambos se convierten en sus correspondientes derivados de ácido carboxílico, nor-

malmente por medio de la acción de un anión hidroxilo (-OH), tal como el que estaría presente en una solución acuosa básica.

El término "grupo saliente," como se usa en este documento, se refiere a un grupo químico funcional que generalmente permite que tenga lugar una reacción de sustitución nucleófila en el átomo al que está unido. Por ejemplo, en cloruros de ácido de la fórmula Cl-C(O)R, donde R es alquilo, arilo, o heterocíclico, el grupo -Cl generalmente se denomina grupo saliente porque permite que tengan lugar reacciones de sustitución nucleófila en el carbono del carbonilo al que está unido. Los especialistas en la técnica conocen los grupos salientes adecuados y pueden incluir haluros, heterocicios aromáticos, ciano, grupos amino (generalmente en condiciones ácidas), grupos amonio, grupos alcóxido, grupos carbonato, formiatos y grupos hidroxi que se han activado por reacción con compuestos tales como carbodiimidas. Por ejemplo, los grupos salientes adecuados pueden incluir, pero sin limitación, grupos cloruro, bromuro yoduro, ciano, imidazol e hidroxi que se han dejado reaccionar con una carbodiimida tal como diciclohexylcarbodiimida (opcionalmente en presencia de un aditivo tal como hidroxibenzotriazol) o un derivado de carbodiimida.

El término "combinación de reactivos," significa un reactivo químico, o más de un reactivo cuando sea necesario, que puede usarse para realizar una reacción química deseada. La elección del reactivo particular, o combinación de reactivos, dependerá de factores que son familiares para los especialistas en la técnica e incluyen, pero sin limitación, la identidad de los reactivos, la presencia de otros grupos funcionales en los reactivos, el disolvente o disolventes usados en una reacción química particular, la temperatura a la que se realizará la reacción química y el método o métodos de purificación del producto de reacción químico deseado. La elección de un reactivo, o combinación de reactivos, necesaria para realizar una reacción química particular están dentro del conocimiento de un especialista en la técnica y tal elección puede realizarse sin excesiva experimentación.

El término "base," como se usa en este documento, significa una base denominada de Bronsted-Lowry. Una base de Bronsted-Lowry es un reactivo que es capaz de aceptar un protón (H^+) a partir de un ácido presente en una mezcla de reacción. Los ejemplos de bases de Bronsted-Lowry incluyen, aunque sin limitación, bases inorgánicas tales como carbonato sódico, bicarbonato sódico, hidróxido sódico, carbonato potásico, bicarbonato potásico, hidróxido potásico y carbonato de cesio, bases inorgánicas tales como trietilamina, diisopropiletilamina, diisopropilamina, diciclohexilamina, morfolina, pirrolidona, piperidina, piridina, 4-N,N-dimetilaminopiridina (DMAP) y imida-

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zol.

La expresión "base quiral no racémica" como se usa en este documento, se refiere a un compuesto básico que puede existir en una forma enantiomérica y que no está presente en una cantidad igual con respecto a su enantiómero opuesto correspondiente. Por ejemplo, el compuesto 2-fenilglicinol existe como dos enantiómeros de configuración opuesta, los enantiómeros denominados (R) y (S). Si los enantiómeros (R) y (S) están presentes en cantidades iguales, se dice que tal mezcla es "racémica." Sin embargo, si un enantiómero está presente en una cantidad mayor que el otro, se dice que la mezcla no es racémica.

El término " estereoisómeros" se refiere a compuestos que tienen una constitución química idéntica, aunque diferente con respecto a la disposición de sus átomos o grupos en el espacio. En particular, el término "enantiómeros" se refiere a dos estereoisómeros de un compuesto que no son imágenes especulares superponibles entre sí. Los términos "racémico" o "mezcla racémica," como se usan en este documento, se refieren a una mezcla 1:1 de enantiómeros de un compuesto particular. El término "diastereómeros", por otro lado, se refiere a la relación entre un par de estereoisómeros que comprende dos o más centros simétricos y que no son imágenes especulares entre sí.

El término producto " estereoquímicamente enriquecido", cuando se usa en este documento, se refiere a un producto de reacción en el que está presente un estereoisómero particular en una cantidad relativa mayor estadísticamente significativa con respecto a los otros productos estereoisoméricos posibles. Por ejemplo, un producto que comprende más de un enantiómero que del otro constituiría un producto enriquecido estereoquímicamente. Análogamente, un producto que comprende más de un diastereoisómero que de los otros constituiría un producto enriquecido estereoquímicamente. Se dice que los métodos y procesos contenidos en este documento dan un producto " estereoquímicamente enriquecido". En tales casos, los métodos y procesos contenidos en este documento empiezan con una mezcla de compuestos estereoisoméricos en la que están presentes todos los posibles estereoisómeros en cantidades aproximadamente iguales y dan un producto en el que está presente al menos un estereoisómero en una cantidad estadísticamente significativa mayor que los otros.

El término "diastereomérico""," como se usa en este documento se refiere a la relación entre un par de estereoisómeros que comprende dos o más centros asimétricos y que no son imágenes especulares superponibles entre sí. Las expresiones "sal diastereomérica," o "sales diastereoméricas," como se usa en este documento signifi-

can una sal de un compuesto diastereomérico, donde "diastereómero" es como se define en este documento.

El término "racémico", como se usa en este documento, significa una composición que comprende una proporción 1:1 de enantiómeros. El término " escalénico," como se usa en este documento, significa una composición que comprende una cantidad desigual de enantiómeros. Por ejemplo, una composición que comprende una mezcla 1:1 de enantiómeros (R) y (S) de un compuesto de la presente invención se denomina composición o mezcla racémica. Como ejemplo adicional, una composición que comprende una mezcla 2:1 de enantiómeros (R) y (S) de un compuesto de la presente invención se denomina una composición o mezcla escalémica. Se contempla específicamente que los métodos de la presente invención puedan usarse ventajosamente para preparar un compuesto escalénico de la presente invención a partir de un compuesto racémico de la presente invención.

Los términos "resolución" y "resolver" se refieren a un método para separar físicamente compuestos estereoisoméricos a partir de una mezcla de estereoisómeros, tales como una mezcla racémica que comprende dos enantiómeros de un compuesto particular. Como se usa en este documento, resolución y "resolver" pretenden incluir tanto resolución parcial como resolución completa.

Los términos "separar" o "separado," como se usa en este documento, se refieren a un proceso de aislamiento físico de al menos dos compuestos químicos diferentes entre sí. Por ejemplo, si una reacción química tiene lugar y produce al menos dos productos, (A) y (B), el proceso de aislamiento de ambos (A) y (B) entre sí se denomina "separar(A) y (B). Se contempla específicamente que las separaciones de la presente invención pueden ser parciales o completas según se determina por técnicas analíticas conocidas por los especialistas en la técnica y las descritas en este documento.

El término "convertir," como se usa en este documento, significa permitir que tenga lugar una reacción química con un material o materiales de partida para producir un producto químico diferente. Por ejemplo, si se deja que los reactivos químicos (A) y (B) reaccionen entre sí para producir el producto (C), puede decirse que los materiales de partida (A) y (B) se han "convertido" en el producto (C), o puede decirse que (A) se "convirtió" en (C), o que (B) se "convirtió" en (C).

La expresión "contraión adecuado", como se usa en este documento, significa un ion o iones de carga opuesta al ion presente en el compuesto o compuestos de la invención, de tal manera que el complejo global o sal tenga una carga neutra. Por ejemplo, si el compuesto de la presente invención contiene una carga global menos 1 (-

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1), un contraión adecuado sería uno con una carga global más 1 (+1) que produciría una carga global neutra para el complejo o la sal. Los ejemplos de contraiones positivos (+) adecuados incluyen, aunque sin limitación, ion sodio (Na^+), ion potasio (K^+), ion cesio (Cs^+) y aminas protonadas (tales como trietilamina protonada, diciclohexilamina protonada, morfolina protonada, o piridina protonada). Como alternativa, si el compuesto de la invención contiene una carga global más 1 (+1), un contraión adecuado sería uno con una carga global menos 1 (-1) que produciría una carga global neutra para el complejo o sal. Los ejemplos de contraiones de carga negativa (-) adecuados incluyen, pero sin limitación, fluoruro (F), cloruro (Cl^-), bromuro (Br^-) yoduro (I^-), hidróxido (^-OH) y acetato ($O\text{-}C(O)CH_3$). También es posible que el contraión adecuado en los compuestos de la presente invención, incluyendo los compuestos usados en los métodos de la presente invención, pueda tener más de una sola carga asociada con ellos. Por ejemplo, si el compuesto de la invención contiene una carga negativa (-1), el contraión adecuado puede contener una carga más dos (+2), de manera que los dos compuestos de la invención con cargas negativas uno están asociados con un contraión adecuado. Los ejemplos de contraiones adecuados con más de una carga positiva incluyen, aunque sin limitación calcio (Ca^{2+}). Finalmente, se contempla también que los compuestos de la presente invención pueden contener más de una carga, de manera que puede ser necesario un contraión adecuado para dar un complejo o sal global neutro. Por ejemplo, el compuesto de la presente invención puede contener más de una carga negativa de uno (-1), de manera que se necesitan dos contraiones adecuados, cada uno con una carga más uno (+1), para dar un complejo o sal global neutro.

El término "sustituido" significa que el grupo o el resto especificado tiene uno o más sustituyentes. El término "no sustituido" significa que el grupo especificado no tiene sustituyentes. El término "sustituido" se refiere a que el grupo especificado está sustituido o no sustituido por uno o más sustituyentes.

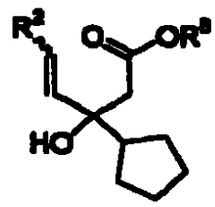
Descripción Detallada

De acuerdo con un convenio usado la técnica, el símbolo  se usa en las fórmulas estructurales de este documento para describir el enlace que es el punto de unión del resto o sustituyente al núcleo o estructura principal. De acuerdo con otro convenio, en algunas fórmulas estructurales de este documento los átomos de carbono y sus átomos de hidrógeno enlazados no se describen explícitamente, por ejemplo,

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 representa un grupo metilo,  representa un grupo etilo,  representa un grupo ciclopentilo, etc.

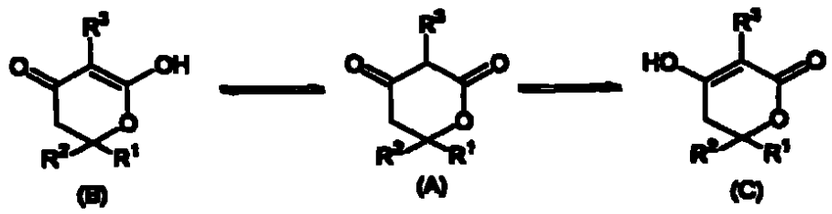
Con respecto a los compuestos de la invención que son alquenos, el símbolo "∿∿∿" se refiere a que puede estar presente el isómero E- o Z, o mezclas de los isómeros E y Z. Por ejemplo, en la estructura mostrada a continuación, el uso del símbolo "∿∿∿" para la unión del grupo R^2 al alqueno,



se refiere a que se consideran representados el isómero E o Z, o mezclas de los isómeros E y Z.

Los compuestos de la presente invención también existen en diferentes formas tautoméricas. Por ejemplo, un compuesto de la invención puede existir en una forma en la que dos cetonas están presentes en un anillo del compuesto, como se muestra a continuación en (A). Como alternativa, los compuestos de la presente invención pueden existir en al menos dos formas de enol diferentes, como se muestra en los compuestos (B) y (C) mostrados a continuación. Estas tres formas pueden estar en equilibrio y los compuestos de la invención pueden existir en más de una de estas formas al mismo tiempo. Por ejemplo, en un compuesto particular de la invención, un cierto porcentaje de las moléculas puede estar presente en la forma (A) mientras que el resto están presentes en la forma (B) o la forma (C). Qué forma predomina en un compuesto particular depende de varios factores que incluyen, pero sin limitación, de si el compuesto está en forma sólida, líquida o cristalina, de si el compuesto se disuelve en un disolvente y de la identidad del disolvente, de la temperatura del medio y de la humedad relativa. Se contempla específicamente que cuando los compuestos de la presente invención se representan en una forma particular, por ejemplo la forma (A), se consideran incluidas todas las formas tautoméricas, por ejemplo las formas (B) y (C).

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(B) (A) (C)

Los compuestos de la presente invención pueden tener átomos de carbono asimétricos. Los enlaces carbono-carbono de los compuestos de la presente invención pueden describirse en este documento usando una línea continua (———), una cuña rellena (▬▬) o una cuña a trazos (▪▪▪▪▪). El uso de un línea continua para describir enlaces a átomos de carbono asimétricos pretende indicar que se incluyen todos los posibles estereoisómeros en el átomo de carbono. El uso de una cuña rellena o a trazos para describir enlaces a átomos de carbono asimétricos pretende indicar que solo se incluye el estereoisómero mostrado. Es posible que los compuestos de la invención puedan contener más de un átomo de carbono asimétrico. En los compuestos, el uso de una línea continua para representar enlaces a átomos de carbono asimétricos se refiere a que indica que se refiere a que están incluidos todos los estereoisómeros posibles. El uso de una línea continua para representar enlaces a uno o más átomos de carbono asimétricos en un compuesto de la invención y el uso de una cuña continua o de puntos para representar enlaces a otros átomos de carbono asimétricos en el mismo compuesto, quiere decir que indica que está presente una mezcla de diastereómeros.

Las soluciones de compuestos estereoisoméricos de la presente invención pueden rotar la luz polarizada en el plano. El uso de cualquiera de los símbolos "(+)" o "(-)" en el nombre de un compuesto de la invención indica que una solución de un estereoisómero particular hace rotar la luz polarizada en el plano en la dirección (+) o (-), medida usando técnicas conocidas por los especialistas en la técnica.

Las mezclas diastereoméricas pueden separarse en sus diastereómeros individuales basándose en sus diferencias fisicoquímicas por métodos conocidos por los especialistas en la técnica, por ejemplo, por cromatografía o cristalización fraccionada. Los enantiómeros se pueden separar transformando las mezclas enantioméricas en una mezcla diasteréomera por reacción con un compuesto ópticamente activo apropiado (por ejemplo, alcohol), separando los diastereómeros y transformando (por ejemplo, hidrolizando) los diasteréomeros individuales a los correspondientes enantiómeros puros. Todos estos isómeros, incluyendo mezclas diastereoméricas y enantiómeros puros se consideran parte de la invención.

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Como alternativa, los compuestos estereoisoméricos individuales de la presente invención pueden prepararse en forma enantioméricamente enriquecida mediante síntesis asimétrica. La síntesis asimétrica puede realizarse usando técnicas conocidas por los especialistas en la técnica, tales como el uso de materiales de partida asimétricos que están disponibles en el mercado o que pueden prepararse fácilmente usando métodos conocidos por los especialistas en la técnica, el uso de compuestos auxiliares asimétricos que pueden retirarse una vez completada la síntesis, o la resolución de compuestos intermedios usando métodos enzimáticos. La elección de tal método dependerá de factores que incluyen, aunque sin limitación, la disponibilidad de los materiales de partida, la eficacia relativa de un método y de si tales métodos son útiles para los compuestos de la invención que contienen grupos funcionales particulares. Tales elecciones están dentro del conocimiento de un especialista en la técnica.

Cuando los compuestos de la presente invención contienen átomos de carbono asimétricos, las sales, profármacos y solvatos derivados pueden existir como estereoisómeros únicos, racematos y/o mezclas de enantiómeros y/o diastereómeros. Se pretende que todos los estereoisómeros únicos, racematos y mezclas de los mismos estén dentro del alcance de la presente invención.

Como se entenderá generalmente por los especialistas en la técnica, un compuesto ópticamente puro es un compuesto que es enantioméricamente puro. Tal y como se emplea en este documento, la expresión ópticamente puro significa un compuesto que comprende al menos una actividad suficiente. Preferiblemente, una cantidad ópticamente pura de un enantiómero sencillo para producir un compuesto que tiene el compuesto farmacológico puro deseado de la invención comprende al menos 90% de un isómero sencillo (80% de exceso enantiomérico), más preferiblemente al menos 95% (90% e.e.), aún más preferiblemente al menos 97,5% (95% e.e.) y aún más preferiblemente, al menos 99% (98% e.e.).

Si un derivado usado en el método de la invención es una base, puede prepararse una sal deseada por cualquier método conocido en la técnica, incluyendo el tratamiento de la base libre con un ácido inorgánico, tal como ácido clorhídrico; ácido bromhídrico; ácido sulfúrico; ácido nítrico; ácido fosfórico; y similares, o con un ácido orgánico, tal como ácido acético; ácido maleico; ácido succínico; ácido mandélico; ácido fumárico; ácido malónico; ácido pirúvico; ácido oxálico; ácido glicólico; ácido salicílico; ácido piranosidílico, tal como ácido glucurónico o ácido galacturónic; alfa-hidroxiácidos, tales como ácido cítrico o ácido tartárico; aminoácidos, tales como ácido aspártico o ácido glutámico; ácidos aromáticos tales como ácido benzoico o ácido ci-

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námico; ácidos sulfónicos, tales como ácido p-toluenosulfónico o ácido etanosulfónico; y similares.

Si un derivado usado en el método de la invención es un ácido, puede prepararse una sal deseada por cualquier método conocido en la técnica, incluyendo tratamiento del ácido libre con una base inorgánica u orgánica, tal como una amina (primaria, secundaria o terciaria); un hidróxido de metal alcalino o alcalinotérreo; o similares. Los ejemplos ilustrativos de sales incluyen sales derivadas de aminoácidos tales como glicina y arginina; de amoniaco; de aminas primarias, secundarias y terciarias; y de aminas cíclicas tales como piperidina, morfolina y piperazina; así como sales inorgánicas derivadas de sodio, calcio, potasio, magnesio, manganeso, hierro, cobre, cinc, aluminio y litio.

En el caso de derivados, profármacos, sales o solvatos que son sólidos, se entenderá por los especialistas en la técnica que los derivados, profármacos, sales y solvatos usados en el método de la invención, pueden existir en diferentes formas polimórficas o cristalinas, todas ellas incluidas dentro del alcance de la presente invención y fórmulas específicas. Además, los derivados, sales, profármacos y solvatos usados en el método de la invención pueden existir como tautómeros, todos ellos incluidos dentro del alcance de la presente invención.

Los compuestos de la presente invención que son básico en la naturaleza son capaces de formar una amplia diversidad de sales diferentes con diversos ácidos inorgánicos y orgánicos. Aunque tales sales deben ser farmacéuticamente aceptables para la administración a animales, a menudo es deseable en la práctica aislar los compuestos de la presente invención a partir de la mezcla de reacción como una sal farmacéuticamente inaceptable y después simplemente convertir esta última en el compuesto base libre por tratamiento con un reactivo alcalino y posteriormente convertir la base libre en una sal de adición de ácidos farmacéuticamente aceptable. Las sales de adición de ácidos de los compuestos básicos de esta invención se preparan fácilmente por tratamiento del compuesto básico con una cantidad sustancialmente equivalente del ácido mineral u orgánico elegido en un medio disolvente acuoso o en un disolvente orgánico adecuado, tal como metanol o etanol. Después de evaporación cuidadosa del disolvente, se obtiene fácilmente la sal sólida deseada. La sal de ácido deseada también puede precipitarse a partir de una disolución de la base libre en un disolvente orgánico mediante la adición a la disolución de un ácido mineral u orgánico apropiado.

Los compuestos de la presente invención que son ácidos en la naturaleza son capaces de formar sales de bases con diversos cationes farmacológicamente acepta-

bles. Los ejemplos de tales sales incluyen las sales de metales alcalinos y de metales alcalinotérreos y particularmente, las sales de sodio y potasio. Todas estas sales se preparan por técnicas convencionales. Las bases químicas que se usan como reactivos para preparar las sales de bases farmacéuticamente aceptables de esta invención son aquellas que forman sales de bases no tóxicas con los compuestos ácidos de la presente invención. Tales sales de bases no tóxicas incluyen las obtenidas a partir de cationes farmacéuticamente aceptables tales como sodio, potasio, calcio, magnesio, etc. Estas sales pueden prepararse fácilmente por tratamiento de los compuestos ácidos correspondientes con una solución acuosa que contiene los cationes farmacológicamente aceptables deseados y después evaporando la solución resultante a sequedad, preferiblemente a presión reducida. Como alternativa, pueden prepararse mezclando soluciones alcanoicas inferiores de los compuestos ácidos junto con el alcóxido de metal alcalino deseado y después evaporando la solución resultante a sequedad de la misma forma que se ha indicado anteriormente. En cualquier caso, es preferible emplear cantidades estequiométricas de los reactivos con el fin de asegurar que se completa la reacción y el máximo rendimiento del producto final deseado.

La actividad de los compuestos como inhibidores de la actividad de HCV puede medirse por cualquiera de los métodos adecuados disponibles en la técnica, incluyendo ensayos *in vivo* e *in vitro*. Un ejemplo de un ensayo adecuado para medir la actividad es el ensayo de replicón de HCV descrito en este documento.

La administración de los compuestos y sus profármacos farmacéuticamente aceptables, sales, metabolitos activos y solvatos puede realizarse de acuerdo con cualquiera de los modos aceptados de administración disponibles para los especialistas en la técnica. Los ejemplos ilustrativos de modos de administración adecuados incluyen la administración oral, nasal, parenteral, tópica, transdérmica y rectal. Los suministros orales e intravenosos son preferidos.

Un agente inhibidor de HCV de la presente invención puede administrarse como una composición farmacéutica en cualquier forma farmacéutica adecuada. Las formas farmacéuticas adecuadas incluyen formulaciones sólidas, semisólidas, líquidas o liofilizadas, tales como comprimidos, polvos, cápsulas, supositorios, suspensiones, liposomas y aerosoles. El agente inhibidor del VHC se puede preparar como una solución empleando cualquiera entre una variedad de metodologías. Por ejemplo, el agente inhibidor de HCV puede disolverse con ácido (por ejemplo, HCl 1 M) y diluirse con un volumen suficiente de una solución de dextrosa al 5% en agua (D5W) para producir la concentración deseada de agente inhibidor de HCV (por ejemplo, aproximadamente 15

mM). Como alternativa, puede usarse una solución de D5W que contiene HCl aproximadamente 15 mM para proporcionar una solución del agente inhibidor de HCV a la concentración apropiada. Además, el agente inhibidor del VHC se puede preparar como una suspensión utilizando, por ejemplo, una solución al 1% de carboximetilcelulosa (CMC).

Los métodos aceptables para preparar formas farmacéuticas adecuadas de las composiciones farmacéuticas son conocidos o pueden determinarse rutinariamente por los especialistas en la técnica. Por ejemplo, las preparaciones farmacéuticas se pueden preparar siguiendo técnicas convencionales de la química farmacéutica que implican etapas tales como mezclar, granular y comprimir cuando sea necesario para formar comprimidos, o mezclar, llenar y disolver los ingredientes de forma adecuada para proporcionar los productos deseados para la administración por vía oral, parenteral, tópica, intravaginal, intranasal, intrabronquial, intraocular, intraaural y/o rectal.

Las composiciones farmacéuticas de la invención también pueden incluir excipientes, diluyentes, vehículos y soportes adecuados, así como otros agentes farmacéuticamente activos, dependiendo del uso deseado. Los vehículos, diluyentes, soportes o excipientes sólidos o líquidos, farmacéuticamente aceptables, se pueden emplear en las composiciones farmacéuticas. Los vehículos sólidos ilustrativos incluyen almidón, lactosa, sulfato cálcico dihidrato, terra alba, sacarosa, talco, gelatina, pectina, goma arábiga, estearato de magnesio y ácido esteárico. Los vehículos líquidos ilustrativos incluyen jarabe, aceite de cacahuete, aceite de oliva, solución salina y agua. El vehículo o el diluyente puede incluir un material adecuado de liberación prolongada, tal como monoestearato de glicerilo o diestearato de glicerilo, solo o con una cera. Cuando se emplea un vehículo líquido, la preparación puede estar en forma de jarabe, elixir, emulsión, cápsula de gelatina blanda, líquido estéril inyectable (p. ej., solución) o una suspensión líquida acuosa o no acuosa.

Una dosis de la composición farmacéutica puede contener al menos una cantidad terapéuticamente eficaz de un agente inhibidor del VHC y preferentemente se prepara con una o varias unidades de dosificación farmacéutica. La dosis seleccionada puede administrarse a un mamífero, por ejemplo, un ser humano en necesidad de tratamiento mediado por la inhibición de la actividad de HCV por cualquier método conocido o adecuado para administrar la dosis, incluyendo tópicamente, por ejemplo, como una pomada o crema; por vía oral; por vía rectal, por ejemplo, como un supositorio; por vía parenteral por inyección; por vía intravenosa; o continuamente por infusión intravaginal, intranasal, intrabronquial, intraaural o intraocular. Cuando la composición se ad-

ministra junto con un fármaco citotóxico, la composición se puede administrar antes, junto con y/o después de introducir el fármaco citotóxico. Sin embargo, cuando la composición se administra junto con radioterapia, la composición preferiblemente se introduce antes de que comience la radioterapia.

Los métodos para preparar las diversas composiciones farmacéuticas con una cantidad específica de compuesto activo se conocen o serán evidentes para los especialistas en esta técnica. Como ejemplos, véase Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15ª Edición (1975).

Se apreciará que las dosificaciones reales de los agentes inhibidores del VHC empleadas en las composiciones farmacéuticas de esta invención, se seleccionarán según las propiedades del agente en particular a utilizar, la composición formulada en particular, el modo de administración y el sitio particular y el hospedador y el estado que se van a tratar. Las dosificaciones óptimas para un grupo de estados dados, las pueden determinar los expertos en la técnica empleando ensayos convencionales para determinar la dosificación. Para la administración oral, por ejemplo, una dosis que puede emplearse es de aproximadamente 0,001 a aproximadamente 1000 mg/kg de peso corporal, de aproximadamente 0,1 a aproximadamente 100 mg/kg de peso corporal, de aproximadamente 1 a aproximadamente 50 mg/kg de peso corporal, o de aproximadamente 0,1 a aproximadamente 1 mg/kg de peso corporal, con cursos de tratamiento repetidos a intervalos apropiados. Las formas de dosificación de las formulaciones farmacéuticas descritas en este documento pueden contener una cantidad de un compuesto de la presente invención, o una sal farmacéuticamente aceptable o solvato del mismo, considerada apropiada por un especialista habitual en la técnica. Por ejemplo, tales formas de dosificación pueden contener de aproximadamente 1 mg a aproximadamente 1500 mg de un compuesto de la presente invención, o pueden contener de aproximadamente 5 mg a aproximadamente 1500 mg, de aproximadamente 5 mg a aproximadamente 1250 mg, de aproximadamente 10 mg a aproximadamente 1250 mg, de aproximadamente 25 mg a aproximadamente 1250 mg, de aproximadamente 25 mg a aproximadamente 1000 mg, de aproximadamente 50 mg a aproximadamente 1000 mg, de aproximadamente 50 mg a aproximadamente 750 mg, de aproximadamente 75 mg a aproximadamente 750 mg, de aproximadamente 100 mg a aproximadamente 750 mg, de aproximadamente 125 mg a aproximadamente 750 mg, de aproximadamente 150 mg a aproximadamente 750 mg, o de aproximadamente 150 mg a aproximadamente 500 mg de un compuesto de la presente invención, o una sal farmacéuticamente aceptable o solvato del mismo.

La presente invención también incluye compuestos marcados con isótopos, que son idénticos a los mencionados en los compuestos de la presente invención, excepto por el hecho de que uno o más átomos se reemplazan por un átomo que tiene una masa atómica o número másico diferente de la masa atómica o número másico encontrado normalmente en la naturaleza. Los ejemplos de isótopos que pueden incorporarse en los compuestos de la invención incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor y cloro, tales como ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F y ^{36}Cl, respectivamente. Los compuestos de la presente invención, sus profármacos y las sales farmacéuticamente aceptables de dichos compuestos o de dichos profármacos, que contienen los isótopos mencionados y/o otros isótopos de otros átomos, están dentro del alcance de esta invención. Ciertos compuestos de la presente invención marcados isotópicamente, por ejemplo aquellos a los que se han incorporado isótopos radiactivos tales como 3H o 14C, son útiles en los ensayos del fármaco y/o de distribución en el tejido sustrato. Los isótopos tritio, es decir, ^{3}H, y carbono-14, es decir, ^{14}C son particularmente preferidos por su facilidad de preparación y detectabilidad. Además, la sustitución con isótopos más pesados tales como deuterio, esto es, 2H, puede proporcionar ciertas ventajas terapéuticas que resultan de la mayor estabilidad metabólica, por ejemplo el aumento de la semi-vida *in vivo* o la reducción de los requerimientos de dosis y por tanto puede ser preferirse en algunas circunstancias. Los compuestos marcados con isótopos de la presente invención y sus profármacos pueden prepararse generalmente realizando los procedimientos descritos en los Esquemas y/o en los Ejemplos y Preparaciones presentados más adelante, sustituyendo un reactivo no marcado con isótopos por un reactivo marcado con isótopos y fácilmente adquirible.

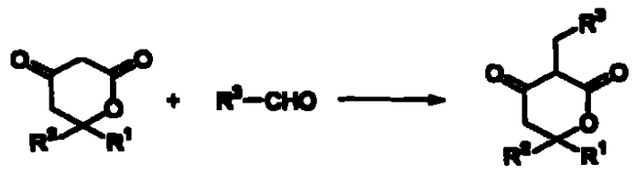
Los compuestos de la presente invención son potentes inhibidores del virus de la Hepatitis C, en particular de la replicación de HCV e incluso más particularmente de la ARN polimerasa dependiente de ARN de HCV. Los compuestos se adaptan al uso terapéutico como agentes anti-HCV en mamíferos, particularmente en seres humanos.

El compuesto activo puede aplicarse como una sola terapia o puede implicar una o más sustancias antivirales distintas, por ejemplo, las seleccionadas entre, por ejemplo, inhibidores de HCV tales como interferón alphacon-1, interferón natural, interferón beta-Ia, interferón omega, interferón gamma-1b, interleuquina-10, BILN 2061 (proteasa de serina), amantadina (Symmetrel), timozina alfa-1, viramidina; inhibidores de VIH tales como nelfinavir, delavirdine, indinavir, nevirapine, saquinavir y tenofovir. Dicho tratamiento conjunto se puede lograr mediante la dosificación simultánea, secuencial o separada de los componentes individuales del tratamiento.

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En general, los compuestos de la presente invención pueden prepararse de acuerdo con los métodos descritos en este documento así como por métodos conocidos por los especialistas habituales en la técnica. Los métodos descritos en este documento no pretenden limitar el alcance de la presente invención de forma alguna y, por lo tanto, no deben considerarse limitantes de dicho alcance.

Los compuestos de fórmula (4) pueden prepararse por reacción de un compuesto de fórmula (11). en la que R^1 y R^2 son como se han definido anteriormente, con un compuesto de fórmula (12), en la que R^3 es como se ha definido anteriormente en este documento.



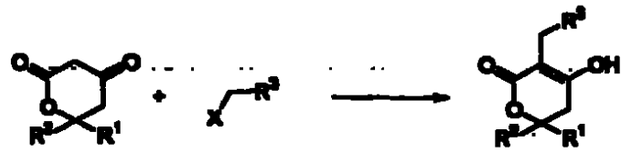
(11) (12) (4)

Generalmente, estas reacciones se realizan en presencia de un agente reductor tal como una fuente de boro o hidrógeno en presencia de un catalizador adecuado. Las fuentes de borano adecuadas incluyen, pero sin limitación, complejo de borano-*trimetilamina*, *complejo de borano-dimetilamina*, *complejo de borano t-butil amina* y complejo de borano-piridina. Los catalizadores adecuados para uso en presencia de un agente reductor tal como hidrógeno incluyen, pero sin limitación, níquel, paladio, rodio y rutenio. Además, tales reacción se realizan en un disolvente o mezcla de disolventes que no interfiera con la reacción química deseada. Además, los disolventes apropiados incluyen los que los especialistas en la técnica saben que son compatibles con las condiciones de reacción e incluyen ésteres de alquilo y ésteres de arilo, éteres de alquilo, heterocíclilo y arilo, hidrocarburos, alcoholes alquílicos y arílicos, compuestos halogenados de alquilo y arilo, nitrilos de alquilo y arilo, cetonas de alquilo y arilo y disolventes heterocíclicos no próticos. Por ejemplo, los disolventes adecuados incluyen, pero sin limitación, acetato de etilo, acetato de isobutilo, acetato de isopropilo, acetato de n-butilo, metil isobutil cetona, dimetoxietano, éter diisopropílico, clorobenceno, dimetil formamida, dimetil acetamida, propionitrilo, butironitrilo, alcohol t-amílico, ácido acético, éter dietílico, metil-t-butil éter, éter difenílico, metilfenil éter, tetrahidrofurano, 2-metiltetrahidrofurano, 1,4-dioxano, pentano, hexano, heptano, metanol, etanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, diclorometano, cloroformo, 1,2-

dicloroetano, acetonitrilo, benzonitrilo, benceno, tolueno, anisol, xilenos y piridina, o cualquier mezcla de los disolventes anteriores. Adicionalmente, puede usarse agua como co-disolvente si no interfiere con la transformación deseada. Finalmente, tales reacciones pueden realizarse a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 75°C, preferiblemente en el intervalo de aproximadamente 0°C a aproximadamente 32°C, más preferiblemente a la temperatura ambiente. La elección de un agente reductor, disolvente y temperatura particular dependerá de diversos factores incluyendo, aunque sin limitación, la identidad de los reactivos particulares y los grupos funcionales presentes en tales reactivos. Tales elecciones están dentro del conocimiento de un especialista en la técnica y pueden realizarse sin excesiva experimentación.

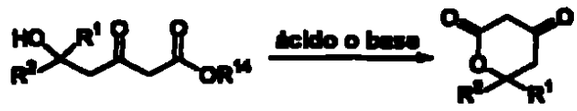
Como alternativa, los compuestos de fórmula (4) pueden prepararse por reacción de un compuesto de fórmula (11) con un compuesto de fórmula (24), en la que X es un grupo saliente adecuado. Los grupos salientes adecuados incluyen, aunque sin limitación, haluros (tales como cloruro, bromuro y yoduro) y ésteres activados (tales como metanosulfonato, trifluorometano sulfonato y ésteres de tosilo). Tales reacciones pueden realizarse en presencia de una base adecuada. Las bases adecuadas incluyen, pero sin limitación, carbonato sódico, bicarbonato sódico, carbonato potásico, carbonato de cesio, hidróxido sódico, hidróxido potásico, hidruro sódico, hidruro de litio, hidruro potásico y diisopropilamida de litio. Además, los disolventes apropiados incluyen aquellos que los especialistas en la técnica saben que son compatibles con las condiciones de reacción e incluyen éteres de alquilo, heterociclilo y de arilo, hidrocarburos, compuestos alquil y aril halógenoados, alquil o aril nitrilos y disolventes heterocíclicos no próticos. Por ejemplo, los disolventes adecuados incluyen, pero sin limitación, dimetoxietano, éter diisopropílico, clorobenceno, dimetil formamida, dimetil acetamida, propionitrilo, butironitrilo, éter dietílico, metil-t-butil éter, éter difenílico, metilfenil éter, tetrahidrofurano, 2-metiltetrahidrofurano, 1,4-dioxano, pentano, hexano, heptano, acetonitrilo, benzonitrilo, benceno, tolueno, anisol, xilenos y piridina, o cualquier mezcla de los disolventes anteriores. Adicionalmente puede usarse agua como co-disolvente si no interfiere con la transformación deseada. Finalmente, tales reacciones pueden realizarse a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 150°C, preferiblemente en el intervalo de aproximadamente 0°C a aproximadamente 32°C, más preferiblemente a la temperatura ambiente. La elección del agente reductor particular, el disolvente y la temperatura dependerán de diversos factores incluyendo, pero sin limitación, la identidad de los reactivos particulares y de los grupos funcionales

presentes en tales reactivos. Tales elecciones están dentro del conocimiento de un especialista en la técnica y pueden realizarse sin excesiva experimentación.



(11) (24) (4)

Los compuestos de fórmula (11), en la que R^1 y R^2 son como se han definido anteriormente, pueden prepararse a partir de compuestos de fórmula (25), por reacción con un ácido o una base adecuados.



(25) (11)

Las bases adecuadas para usar en estas reacciones incluyen bases inorgánicas y bases orgánicas. Las bases inorgánicas adecuadas incluyen, aunque sin limitación, carbonato sódico, bicarbonato sódico, carbonato potásico, bicarbonato potásico, hidróxido sódico, hidruro sódico, hidruro potásico y carbonato de cesio. Preferiblemente, la base es carbonato potásico. Las bases orgánicas adecuadas incluyen, pero sin limitación, piridina, trietilamina, tributilamina, trietanolamina, N-metilmorfolina, Netil-N,N-diisopropilamina, DBU y 4-N,N-dimetilaminopiridina. Estas reacciones también pueden realizarse en presencia de una cantidad catalítica de un ácido adecuado. Los ácidos adecuados incluyen tanto ácidos de Bronsted-Lowry como ácidos de Lewis. Además, estas reacción se realizan generalmente en un disolvente o mezcla de disolventes que no interfiera con la reacción química deseada. Además, los disolventes apropiados incluyen los que los especialistas en la técnica saben que son compatibles con las condiciones de reacción e incluyen ésteres de alquilo y ésteres de arilo, éteres de alquilo, heterociclilo y arilo, hidrocarburos, alcoholes alquílicos y arílicos, compuestos halógenoados de alquilo y arilo, nitrilos de alquilo y arilo, cetonas de alquilo y arilo y disolventes heterocíclicos no próticos. Por ejemplo, los disolventes adecuados incluyen, pero sin limitación, acetato de etilo, acetato de isobutilo, acetato de isopropilo, acetato de n-butilo, metil isobutil cetona, dimetoxietano, éter diisopropílico, clorobenceno, dimetil

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formamida, dimetil acetamida, propionitrilo, butironitrilo, alcohol t-amílico, ácido acético, éter dietílico, metil-t-butil éter, éter difenílico, metilfenil éter, tetrahidrofurano, 2-metiltetrahidrofurano, 1,4-dioxano, pentano, hexano, heptano, metanol, etanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, diclorometano, cloroformo, 1,2-dicloroetano, acetonitrilo, benzonitrilo, acetona, 2-butanona, benceno, tolueno, anisol, xilenos y piridina, o cualquier mezcla de los disolventes anteriores. Adicionalmente puede usarse agua como co-disolvente si no interfiere con la transformación deseada. Finalmente, tales reacciones pueden realizarse a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 100°C, o en el intervalo de aproximadamente 25°C a aproximadamente 100°C, o en el intervalo de aproximadamente 35°C a aproximadamente 75°C, o en intervalo de aproximadamente 45°C a aproximadamente 55°C, o a aproximadamente 50°C. La elección de un agente reductor particular, del disolvente y de la temperatura dependerá de diversos factores incluyendo, aunque sin limitación, la identidad de los reactivos particulares y los grupos funcionales presentes en tales reactivos. Tales elecciones están dentro del conocimiento de un especialista habitual en la técnica y pueden realizarse sin una experimentación excesiva.

Como alternativa, los compuestos de fórmula (11), en la que R^1 y R^2 son como se han definido anteriormente en este documento, pueden prepararse a partir de compuestos de fórmula (25), en la que R^{14} es hidrógeno, por reacción con un reactivo adecuado, o una combinación de reactivos adecuados, para realizar la ciclación. Tales reacciones pueden realizarse en presencia de un reactivo o combinación de reactivos que conviertan el grupo carboxílico -OH en un grupo saliente adecuado, tal como por ejemplo cloro o un grupo imidazol. El término "un grupo saliente adecuado" se refiere a un grupo químico que es capaz de desplazarse cuando un grupo nucleófilo adecuado tal como un grupo hidroxilo reaccione con el carbono del carbonilo en el grupo carboxilo en los compuestos de fórmula (25). Tales grupos salientes adecuados pueden introducirse en los compuestos de fórmula (25) en la que R^{14} es hidrógeno, por reacción del compuesto de fórmula (25) con un reactivo o combinación de reactivos adecuados conocidos por los especialistas habituales en la técnica. Por ejemplo, un compuesto de fórmula (25), en la que R^{14} es hidrógeno, puede dejarse reaccionar con fosgeno (ClC(O)Cl) o trifosgeno ($(Cl)_3C(O)C(Cl)_3$) para producir el un denominado cloruro de ácido, que es aquel en el que el grupo hidroxilo del carboxi se ha sustituido por un átomo de cloro. Además, los compuestos de fórmula (25) pueden convertirse en compuestos en los que el grupo hidroxilo del carboxi se sustituye por otro tipo de grupo saliente adecuado, tal como un grupo imidazol. Tales compuestos pueden prepararse usando

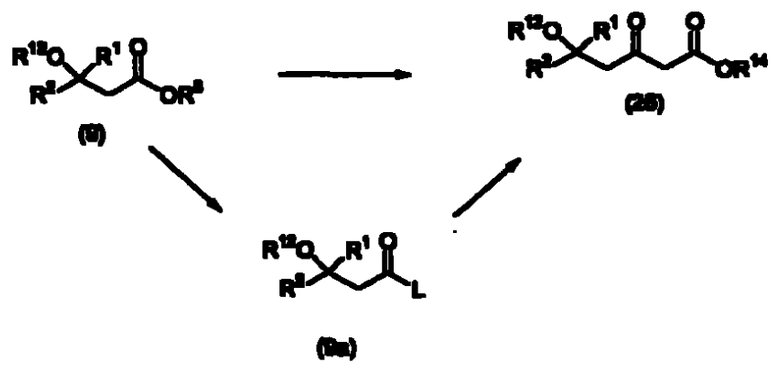
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un reactivo o combinación de reactivos adecuados tal como carbonil diimidazol. Este tipo de reacciones puede realizarse en presencia de una base adecuada, tal como por ejemplo trietilamina y en un disolvente aprótico que no interfiera con la reacción química deseada, por ejemplo cloroformo o diclorometano. Además, tales reacciones pueden realizarse a una temperatura en el intervalo de aproximadamente -78°C a aproximadamente 75°C, o en el intervalo de aproximadamente 0°C a aproximadamente 50°C, o de aproximadamente 0°C a aproximadamente 25°C. La elección de un reactivo adecuado para convertir el grupo carboxilo en un cloruro de ácido, por ejemplo, un disolvente adecuado y una temperatura adecuada son todas elecciones dentro del conocimiento de un especialista en la técnica y pueden realizarse sin excesiva experimentación.

Los compuestos de fórmula (25), en la que el grupo hidroxilo del carboxi se ha convertido en un grupo saliente apropiado, por ejemplo en cloruro de ácido, pueden convertirse en compuestos de fórmula (11) por reacción en presencia de una base adecuada. Las bases adecuadas incluyen, aunque sin limitación, bases inorgánicas y bases orgánicas. Las bases inorgánicas adecuadas incluyen, aunque sin limitación, carbonato sódico, bicarbonato sódico, carbonato potásico, bicarbonato potásico y carbonato de cesio. Las bases orgánicas adecuadas incluyen, pero sin limitación, piridina y 4-N,N-dimetilaminopiridina. Además, los disolventes apropiados incluyen aquellos que son conocidos por los especialistas en la técnica por ser compatibles con las condiciones de reacción e incluyen ésteres de alquilo y ésteres de arilo, éteres de alquilo, heterocicilo y arilo, hidrocarburos, alcoholes de alquilo y arilo, compuestos de alquilo y arilo halogenados, nitrilo alquilo y arilo, cetonas de alquilo y arilo y disolventes heterocíclicos no próticos. Por ejemplo, los disolventes adecuados incluyen, pero sin limitación, acetato de etilo , acetato de isobutilo, acetato de isopropilo, acetato de n-butilo, metil isobutil cetona, dimetoxietano, éter diisopropílico, clorobenceno, dimetil formamida, dimetil acetamida, propionitrilo, butironitrilo, alcohol t-amílico, ácido acético, éter dietílico, metil-t-butil éter, éter difenílico, metilfenil éter, tetrahidrofurano, 2-metiltetrahidrofurano, 1,4-dioxano, pentano, hexano, heptano, metanol, etanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, diclorometano, cloroformo, 1,2-dicloroetano, acetonitrilo, benzonitrilo, acetona, 2-butanona, benceno, tolueno, anisol, xilenos y piridina, o cualquier mezcla de los disolventes anteriores. La elección del agente de activación particular, del disolvente, de la base y de la temperatura para realizar la transformación deseada están dentro del conocimiento de un especialista habitual en la técnica y pueden realizarse sin una experimentación excesiva.

Los compuestos de fórmula (25), en la que R^1 y R^2 son como se han definido anterior-

mente en este documento, P^1 es hidrógeno o un grupo protector adecuado y R^{14} es alquilo C_1-C_6, -Si(alquilo C_1-C_6)$_3$, o -CH_2(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$, pueden prepararse a partir de compuestos de fórmula (9), en la que R^1 y R^2 son como se han definido anteriormente en este documento, R^{12} es hidrógeno o -C(O)R^{13} y R^{13} es hidrógeno, alquilo C_1-C_6, -Si(alquilo C_1-C_6)$_3$, o -CH_2(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$, o a partir de compuesto de fórmula (9a), en la que R^1, R^2 y R^{12} son como se han definido anteriormente en este documento y L es un grupo saliente adecuado, como se muestra a continuación.



El compuesto de fórmula (9) en la que R^9 es hidrógeno puede dejarse reaccionar con un reactivo o combinación de reactivos que conviertan el grupo hidroxilo del carboxi en un grupo saliente adecuado -OA. Tales grupos incluyen ésteres activados, tales como diversos ésteres de benzoílo, tales como un 2,6-dinitrobenzoil éster o un perfluorobenzoil éster, anhídridos mixtos, o un intermedio derivado de la reacción del grupo caboxi con una carbodiimida, tal como dietil carbodiimida o diisopropil carbodiimida. Estos compuestos pueden prepararse por reacción del grupo carboxi con un reactivo adecuado, tal como una carbodiimida, en un disolvente que no interfiera con la reacción química deseada, tal como cloroformo, diclorometano o tetrahidrofurano y a una temperatura de aproximadamente -78°C a aproximadamente 100°C, o en el intervalo de aproximadamente 0°C a aproximadamente 75°C, o en el intervalo de aproximadamente 0°C a aproximadamente 50°C. El compuesto de fórmula (9) que contiene el grupo saliente adecuado -OA puede aislarse o puede dejarse reaccionar en la siguiente etapa sin ninguna purificación adicional. El compuesto que contiene el grupo

saliente adecuado -OA después puede dejarse reaccionar con un reactivo o combinación de reactivos para proporcionar el compuesto de fórmula (25). Tales reactivos adecuados incluyen, aunque sin limitación, aniones malonato provenientes de la desprotonación de un derivado de malonato con una base adecuada y ésteres de malonato de magnesio, tales como malonato de metil magnesio y malonato de etil magnesio. Además, los disolventes apropiados incluyen los que los especialistas en la técnica saben que son compatibles con las condiciones de reacción e incluyen ésteres de alquilo y ésteres de arilo, éteres de alquilo, heterocíclilo y arilo, hidrocarburos, alcoholes alquílicos y arílicos, compuestos halógenoados de alquilo y arilo, nitrilos de alquilo y arilo, cetonas de alquilo y arilo y disolventes heterocíclicos no próticos. Por ejemplo, los disolventes adecuados incluyen, pero sin limitación, acetato de etilo, acetato de isobutilo, acetato de isopropilo, acetato de n-butilo, metil isobutil cetona, dimetoxietano, éter diisopropílico, clorobenceno, dimetil formamida, dimetil acetamida, propionitrilo, butironitrilo, alcohol t-amílico, ácido acético, éter dietílico, metil-t-butil éter, éter difenílico, metilfenil éter, tetrahidrofurano, 2metiltetrahidrofurano, 1,4-dioxano, pentano, hexano, heptano, metanol, etanol, 1-propanol, 2-propano], t-butanol, n-butanol, 2-butanol, diclorometano, cloroformo, 1,2-dicloroetano, acetonitrilo, benzonitrilo, acetona, 2-butanona, benceno, tolueno, anisol, xilenos y piridina, o cualquier mezcla de los disolventes anteriores. Además, puede realizarse a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 150°C, o en el intervalo de aproximadamente 0°C a aproximadamente 75°C, o en el intervalo de aproximadamente 20°C a aproximadamente 75°C, o en el intervalo de aproximadamente 25°C a aproximadamente 50°C, o a aproximadamente 40°C. La elección particular del reactivo o combinación de reactivos, disolvente o disolventes y temperatura están dentro del conocimiento de un especialista en la técnica y pueden realizarse sin excesiva experimentación.

Como alternativa, los compuestos de fórmula (25) pueden prepararse a partir de compuestos de fórmula (9), en la que R^8 es alquilo C_1-C_6, -Si(alquilo C_1-C_6)$_3$, o -CH_2(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$, por reacción con un reactivo o combinación de reactivos para proporcionar el compuestos de fórmula (III). Tales reactivos adecuados incluyen, aunque sin limitación ésteres de malonato de magnesio, tales como malonato de metil magnesio y malonato de etil magnesio. Tales reactivos adecuados incluyen, aunque sin limitación, aniones malonato provenientes de la desprotonación de un derivado de malonato con una base adecuada y ésteres de malonato de magnesio, tales como malonato de metil

magnesio y malonato de etil magnesio. Además, los disolventes adecuados incluyen los conocidos por los especialistas en la técnica por ser compatibles con las condiciones de reacción e incluyen ésteres de alquilo y ésteres de arilo, éteres de alquilo, heterociclilo y arilo, alcoholes de alquilo y arilo, compuestos de alquilo y arilo halogenados, nitrilos de alquilo o arilo, cetonas de alquilo o arilo y disolventes heterocíclicos no próticos. Por ejemplo, los disolventes adecuados incluyen, pero sin limitación, acetato de etilo, acetato de isobutilo, acetato de isopropilo, acetato de n-butilo, metil isobutil cetona, dimetoxietano, diisopropil éter, clorobenceno, dimetil formamida, dimetil acetamida, propionitrilo, butironitrilo, alcohol t-amílico, ácido acético, éter dietílico, metil-t-butil éter, éter difenílico, metilfenil éter, tetrahidrofurano, 2metiltetrahidrofurano, 1,4-dioxano, pentano, hexano, heptano, metanol, etanol, 1-propanol, 2propanol, t-butanol, n-butanol, 2-butanol, diclorometano, cloroformo, 1,2-dicloroetano, acetonitrilo, benzonitrilo, acetona, 2-butanona, benceno, tolueno, anisol, xilenos y piridina, o cualquier mezcla de los disolventes anteriores. Además, puede realizarse a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 150°C, o en el intervalo de aproximadamente 0°C a aproximadamente 75°C, o en el intervalo de aproximadamente 20°C a aproximadamente 75°C, o en el intervalo de aproximadamente 25°C a aproximadamente 50°C, o a aproximadamente 40°C. La elección particular del reactivo o combinación de reactivos, disolvente o disolventes y temperatura, está dentro del conocimiento de un *especialista habitual en la técnica y puede realizarse sin una experimentación excesiva.*

Además, los compuestos de fórmula (25) pueden prepararse a partir de compuestos de fórmula (9a), en la que R^1, R^2 y R^{12} son como se han definido anteriormente en este documento y L es un grupo saliente adecuado, con un reactivo o combinación de reactivos para proporcionar el compuesto de fórmula (25). Los grupos salientes adecuados incluyen, pero sin limitación, cloruro, bromuro yoduro e imidazol. Los compuestos con grupos salientes adecuados pueden prepararse a partir de compuestos de fórmula (9) en la que R^6 es -OH por reacción con un reactivo de activación o combinación de reactivos de activación capaces de sustituir el grupo hidroxilo del carboxi por L. Tales reactivos de activación incluyen, pero sin limitación, cloruro de tionilo ($SOCl_2$), fosgeno, trifosgeno y carbonildiimidazol. Estas reacciones se realizan típicamente en presencia de una base que no interfiera con la reacción química deseada, tal como trietilamina, etildiisopropilamina, piridina, o 4-N,N-dimetilaminopiridina. Además, las reacciones se realizan en un disolvente aprótico que no interfiera con la reacción química deseada tal como por ejemplo tetrahidrofurano, metilbutil éter, éter diisopropílico, éter dietílico, tolueno, cloroformo, diclorometano, o 1,2-dicloroetano. Además, tales

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reacciones se realizan a una temperatura en el intervalo de aproximadamente -78°C a aproximadamente 100°C, o en el intervalo de aproximadamente -50°C a aproximadamente 100°C, o en el intervalo de aproximadamente 0°C a aproximadamente 75°C, o en el intervalo de aproximadamente 0°C a aproximadamente 50°C, o en el intervalo de aproximadamente 0°C a aproximadamente 25°C. Después de la conversión de un compuesto de fórmula (9) en un compuesto de fórmula (9a), el compuesto de fórmula (9a) puede dejarse reaccionar con un reactivo o combinación de reactivos capaces de convertir el compuesto de fórmula (9a) en uno de fórmula (25). tales reactivos adecuados incluyen, aunque sin limitación ésteres de malonato de magnesio, tales como malonato de metil magnesio y malonato de etil magnesio. Estas reacciones se realizan en un disolvente o mezcla de disolventes que no interfiera con la reacción química deseada, tal como éter dietílico, metil t-butil éter y tetrahidrofurano, o mezclas de los mismos. Además, se realizan a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 100°C, o en el intervalo de aproximadamente 0°C a aproximadamente 75°C, o en el intervalo de aproximadamente 20°C a aproximadamente 75°C, o en el intervalo de aproximadamente 25°C a aproximadamente 50°C, o a aproximadamente 40°C. La elección particular del reactivo o combinación de reactivos, disolvente o disolventes y temperatura están dentro del conocimiento de un especialista en la técnica y pueden realizarse sin excesiva experimentación.

La reacción de compuestos de fórmula (9), (9a), o derivados adecuadamente activados de los mismos, con un reactivo o combinación de reactivos para producir un compuesto de fórmula (25) puede requerir la introducción de un grupo protector adecuado para el grupo hidroxilo terciario en los compuestos de fórmula (9). Tales grupos protectores deben ser capaces de introducirse en el compuesto de fórmula (9) en condiciones que protegen selectivamente dicho grupo hidroxilo. Tales reactivos y condiciones son bien conocidas para los especialistas en la técnica y pueden encontrarse, por ejemplo, en T. Greene y P. Wuts, *Protective Groups in Organic Synthesis* (3ª ed.), John Wiley & Sons, NY (1999). Por ejemplo, un grupo sililo protector, tal como un grupo triisopropilsililo, puede introducirse en el compuesto de fórmula (9) para proteger selectivamente el grupo hidroxilo terciario. Dicho grupo puede introducirse usando un reactivo de silano adecuado, tal como por ejemplo cloruro de triisopropil sililo, en presencia de una base, tal como por ejemplo trietilamina y en un disolvente aprótico, por ejemplo cloroformo. El compuesto de fórmula (9) protegido después puede hacerse reaccionar como se ha descrito anteriormente para producir un compuesto de fórmula (25) en forma protegida. El compuesto protegido (25) después puede desprotegerse usando con-

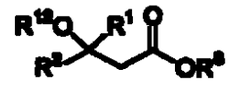
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diciones conocidas por los especialistas en la técnica. Por ejemplo, si el grupo hidroxilo terciario en el compuesto de fórmula (25) se protege, por ejemplo, con un éter de sililo, éste puede desprotegerse usando una fuente de fluoruro, por ejemplo fluoruro de tetrabutilamonio, en un disolvente tal como THF y a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 100°C, o en el intervalo de aproximadamente 0°C a aproximadamente 25°C. Si el grupo hidroxilo terciario en el compuesto de fórmula (9) requiere protección antes de la conversión en el compuesto de fórmula (25) está dentro del conocimiento de un especialista habitual en la técnica y dicha elección puede realizarse sin una experimentación excesiva.

Los reactivos tales como ésteres de malonato de magnesio, por ejemplo malonato de metil magnesio o malonato de etil magnesio, están disponibles en el mercado o pueden prepararse usando métodos conocidos por los especialistas en la técnica. Por ejemplo, puede prepararse malonato de etil magnesio por reacción de etóxido de magnesio con ácido etilmalónico, como se muestra a continuación.



Los compuestos de fórmula (9), en la que R^1, R^2 y R^{12}, son como se han definido anteriormente en este documento y R^8 es hidrógeno, pueden prepararse a partir de compuestos de fórmula (9),

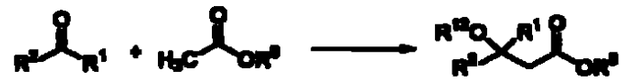


(9)

en la que R^8 es alquilo C_1-C_6, -Si(alquilo C_1-C_6)$_3$, o -CH_2(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$, por hidrólisis con un ácido o base adecuado en un disolvente acuoso. Las bases adecuadas incluyen, aunque sin limitación, hidróxido de litio, hidróxido sódico, hidróxido potásico, carbonato sódico y carbonato potásico. Los ácidos adecuados incluyen, aunque sin limitación, ácido clorhídrico, ácido bromhídrico, ácido yodhídrico y ácido sulfúrico. estas reacciones pueden realizarse en un disolvente o mezcla de disolventes que no interfiera con la reacción química deseada incluyendo, aunque sin limitación, éter dietílico, metil terc-

butil éter, tetrahidrofurano, alcohol metílico, alcohol etílico, alcohol iso-propílico, alcohol n-propílico y alcohol terc-butílico. Puede usarse agua ventajosamente como co-disolvente en estas reacciones. Además, estas reacciones típicamente se realizan a una temperatura en el intervalo de aproximadamente -78°C a aproximadamente 50°C, o en el intervalo de aproximadamente -35°C a aproximadamente 50°C, o en el intervalo de aproximadamente -35°C a aproximadamente 25°C.

Los compuestos de fórmula (9), en la que R^1, R^2 y R^{12} son como se han definido anteriormente en este documento y R^9 es hidrógeno, alquilo C_1-C_6, -Si(alquilo C_1-C_6)$_3$, o -CH_2(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$, pueden prepararse por reacción de un compuesto de fórmula (26), en la que R^1 y R^2 son como se han definido anteriormente en este documento, con un compuesto de fórmula (14), en la que R^9 es hidrógeno, alquilo C_1-C_6, -Si(alquilo C_1-C_6)$_3$, o -CH_2(arilo C_6-C_{10}), donde dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$, como se muestra a continuación

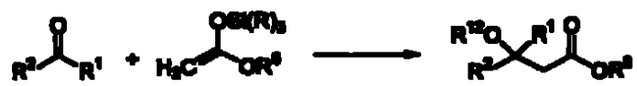


(26) (14) (9)

Estas reacciones pueden realizarse en presencia de una base fuerte para reaccionar en primer lugar con el compuesto de fórmula (14) para producir un anión. Las bases fuertes adecuadas para tales reacciones incluyen hexametil disilazida de litio (LiHMDS), hexametil disilazida de sodio, hexametil disilazida de potasio, diisopropil amida de litio y diisopropilamida de magnesio. Además, tales reacciones pueden realizarse en presencia de un disolvente que no interfiera con la reacción química deseada. Los disolventes adecuados incluyen, pero sin limitación, soluciones puras del compuesto de fórmula (14), éter dietílico, metil terc-butil éter y tetrahidrofurano. Además, tales reacciones pueden realizarse a una temperatura en el intervalo de aproximadamente -78°C a aproximadamente 25°C, o en el intervalo de aproximadamente -50°C a aproximadamente 25°C, o de aproximadamente -35°C a aproximadamente 25°C, o en el intervalo de aproximadamente -35°C a aproximadamente 0°C.

Como alternativa, los compuestos de fórmula (9) pueden prepararse por reacción de un compuesto de fórmula (26) con un sililceteno acetal como se muestra conti-

nuación, en el que R es, por ejemplo, un grupo alquilo C_1-C_6 y R^8 es como se ha definido anteriormente en este documento. Estas reacciones pueden realizarse en presencia de una cantidad catalítica o estequiométrica de un ácido de Lewis adecuado que incluye, pero sin limitación, cloruro de aluminio (III), cloruro de titanio (II), cloruro de titanio (IV), cloruro de estaño (II) y cloruro de estaño (IV). Además, tales reacciones pueden realizarse en presencia de un disolvente que no interfiera con la reacción química deseada. Los disolventes adecuados incluyen, pero sin limitación, éter dietílico, metil terc-butil éter y tetrahidrofurano. Además, tales reacciones pueden realizarse a una temperatura en el intervalo de aproximadamente -78°C a aproximadamente 25°C, o en el intervalo de aproximadamente -50°C a aproximadamente 25°C, o de aproximadamente -35°C a aproximadamente 25°C, o en el intervalo de aproximadamente -35°C a aproximadamente 0°C.



(28) (9)

Los compuestos de fórmula (9), en la que R^1, R^2 y R^{12} son como se han definido anteriormente en este documento y R^8 es hidrógeno pueden resolverse o enriquecerse estereoisoméricamente. Tales compuestos pueden enriquecerse estereoisoméricamente dejándolos después que reaccionen con una base quiral no racémica para formar una mezcla de sales diastereoméricas. Tales sales diastereoméricas pueden separarse después usando técnicas bien conocidas por los especialistas en la técnica, tales como cristalización fraccionada. Por ejemplo, una mezcla de las sales diastereoméricas puede disolverse en un disolvente adecuado y una sal diastereomérica puede cristalizarse después en la solución después de lo cual puede recogerse, lavarse y secarse. Las bases quirales adecuadas, no racémicas incluyen aminas básicas que incluyen, aunque sin limitación, un enantiómero de cis-1-amino-2-indanol, cinconidina, 1-aminoindano, terc-leucinol, 2-amino-1,2-difeniletanol y alfa-metilbencilamina. Por ejemplo, un compuesto de fórmula (9), en la que R^1, R^2 y R^{12} son como se han definido anteriormente en este documento y R^8 es hidrógeno, puede dejarse reaccionar con (1 R,2S)-(+)-cis-1-amino-2-indanol en un disolvente adecuado, tal como tetrahidrofurano para producir una mezcla de sales diastereoméricas. La solución que contiene la mezcla de sales diastereoméricas después puede dejarse enfriar lentamente de forma que sólo una de las sales diastereoméricas sea apreciablemente soluble en el disolvente

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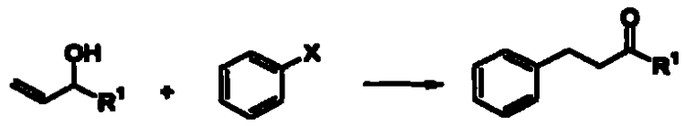
enfriado. La sal diastereomérica restante puede precipitarse después fuera de la solución en forma de un sólido cristalino que comprende una sal diastereomérica en forma sustancialmente pura. El compuesto enriquecido estereoisoméricamente deseado de fórmula (9) después puede obtenerse a partir de la sal diastereomérica precipitada o a partir de la sal diastereomérica que permanece en la solución. El compuesto de fórmula (9), en la que R^9 es hidrógeno, después puede obtener a partir de la sal diastereomérica sustancialmente pura por reacción con un compuesto ácido adecuado, tal como ácido cítrico.

Los compuestos de fórmula (14), en la que R^9 es hidrógeno, alquilo C_1-C_6, -Si(alquilo C_1-C_6)$_3$, o -CH_2(arilo C_6-C_{10}), en la que dicho grupo arilo C_6-C_{10} está opcionalmente sustituido con al menos un sustituyente seleccionado entre halógeno, alquilo C_1-C_6, -OH, -OCH_3 y -N(alquilo C_1-C_6)$_2$, están disponibles en el mercado o pueden prepararse de acuerdo con métodos conocidos por los especialistas habituales en la técnica.

Los compuestos de fórmula (26) pueden prepararse mediante la denominada reacción de tipo Heck. Por ejemplo, el compuesto de fórmula (26), en la que R^1 es como se ha definido anteriormente en este documento y R^2 es -$(CH_2)_2$Ph, pueden prepararse a partir de la reacción de compuestos de fórmula (27) con un compuesto de fórmula (28), en la que X es un grupo adecuado para uso en una reacción de acoplamiento de tipo Heck catalizada con paladio (Pd-catalizada). Las reacciones de acoplamiento de tipo Heck pueden realizarse usando un catalizador basado en paladio. Los catalizador adecuados incluyen, aunque sin limitación, $Pd(OAc)_2$, $PdCl_2$ y $Pd(PPh_3)_4$. Además, tales reacciones pueden realizarse en presencia de una base, tal como trietilamina, acetato sódico, acetato de litio, acetato potásico, carbonato sódico, carbonato potásico, o carbonato de cesio. Estas reacciones pueden realizarse en un disolvente que no interfiera con la reacción química deseada. Además, los disolventes apropiados incluyen los que los especialistas en la técnica saben que son compatibles con las condiciones de reacción e incluyen ésteres de alquilo y ésteres de arilo, éteres de alquilo, heterociclilo y arilo, hidrocarburos, alcoholes alquílicos y arílicos, compuestos halógenoados de alquilo y arilo, nitrilos de alquilo y arilo, cetonas de alquilo y arilo, amidas y disolventes heterocíclicos no próticos. Por ejemplo, los disolventes adecuados incluyen, pero sin limitación, acetato de etilo, acetato de isobutilo, acetato de isopropilo, nbutil acetato, metil isobutil cetona, dimetoxietano, éter diisopropílico, clorobenceno, dimetil formamida, dimetil acetamida, propionitrilo, butironitrilo, alcohol t-amílico, ácido acético, éter dietílico, metil-t-butil éter, éter difenílico, N-metilpirrolidinona, metilfenil éter, tetrahidrofu-

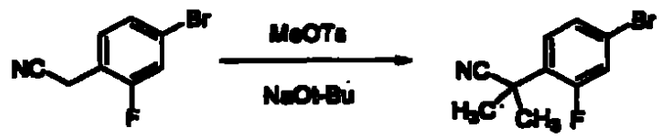
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rano, 2metiltetrahidrofurano, 1,4-dioxano, pentano, hexano, heptano, metanol, etanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, diclorometano, cloroformo, 1,2-dicloroetano, acetonitrilo, benzonitrilo, acetona, 2-butanona, benceno, tolueno, anisol, xilenos y piridina, o cualquier mezcla de los disolventes anteriores. Además, estas reacciones pueden realizarse a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 150°C, o en el intervalo de aproximadamente 25°C a aproximadamente 150°C, o en el intervalo de aproximadamente 25°C a aproximadamente 100°C, o en el intervalo de aproximadamente 45°C a aproximadamente 100°C, o en el intervalo de aproximadamente 45°C a aproximadamente 75°C. Por último, en los compuestos de fórmula (28), X es un grupo que es adecuado para uso en las reacciones de tipo Heck. Los grupos adecuados incluyen cloruro, bromuro yoduro y triflato ($-OSO_2CF_3$).



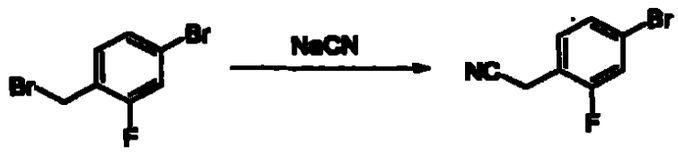
(27) (28) (29)

Los compuestos de fórmula (28) están disponibles en el mercado o pueden prepararse por métodos conocidos por los especialistas habituales en la técnica. Por ejemplo, el 2-(4-bromo-2-fluorofenil)-2metilpropanonitrilo, compuesto (28a) puede prepararse a partir de (4-bromo-2-fluorofenil)acetonitrilo, compuesto (28b), por reacción con un agente de alquilación, por ejemplo tosilato de metilo, en presencia de una base, por ejemplo t-butóxido sódico, como se muestra a continuación.

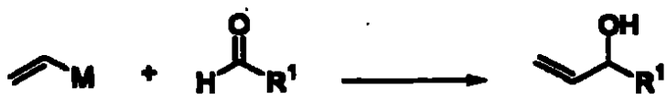


(28B) (28A)

Además, (4-bromo-2-fluorofenil)acetonitrilo puede prepararse a partir de 4-bromo-1-(bromometil)-2-fluorobenceno por reacción con una sal de cianuro, por ejemplo cianuro sódico, como se muestra a continuación.



Los compuestos de fórmula (27), en la que R^1 es como se ha definido anteriormente en este documento, pueden prepararse por reacción de compuestos de fórmula (29), en la que R^1 es como se ha definido anteriormente en este documento y un compuesto de fórmula (30),



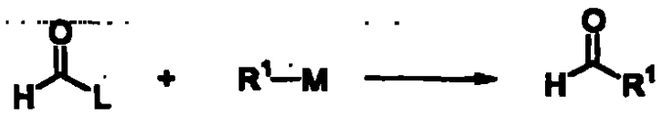
(30) (29) (27)

donde M es un metal adecuado, como se muestra. En los compuestos de fórmula (30), M se elige entre un metal adecuado, tal como un derivado de magnesio, tal como bromuro de magnesio, o litio. Estas reacciones pueden realizarse en un disolvente aprótico, tal como por ejemplo éter dietílico, metil terc-butil éter, o tetrahidrofurano. Además, estas reacciones pueden realizarse a una temperatura en el intervalo de aproximadamente -78°C a aproximadamente 50°C, o en el intervalo de aproximadamente -78°C a aproximadamente 25°C, o en el intervalo de aproximadamente -78°C a aproximadamente 0°C.

Los compuestos de fórmula (30), en la que M es un grupo metálico adecuado, están disponibles en el mercado o pueden prepararse por métodos conocidos por los especialistas habituales en la técnica. Por ejemplo, el compuesto de fórmula (30) en la que M es -MgBr pueden prepararse a partir de bromuro de vinilo y un precursor de magnesio adecuado, tal como metal magnesio o magnesio Reike activado. Estas reacciones pueden realizarse en un disolvente prótico tal como éter dietílico, metil terc-butil éter, o tetrahidrofurano y a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 25°C. Los compuestos de fórmula (30) en la que M es Li pueden prepararse a partir de haluros de vinilo, tales como bromuro o yoduro de vinilo en un reactivo de alquil litio adecuado, tal como butil litio o terc-butil litio. Estas reacciones pueden realizarse en un disolvente prótico tal como éter dietílico, metil terc-butil éter, o tetrahidrofurano y a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 25°C.

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Los compuestos de fórmula (29), en la que R^1 es como se ha definido anteriormente, están disponibles en el mercado o pueden prepararse por reacción de un compuesto de fórmula (32), en la que R^1 es como se ha definido anteriormente y M es un metal adecuado. En los compuestos de fórmula (31), L es un grupo saliente adecuado, tal como un grupo $-N(CH_3)_2$. En los compuestos de fórmula (32), M es un metal adecuado tal como -MgBr o Li. Estas reacciones pueden realizarse en un disolvente aprótico tal como éter dietílico, metil terc-butil éter, o tetrahidrofurano y a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 25°C.



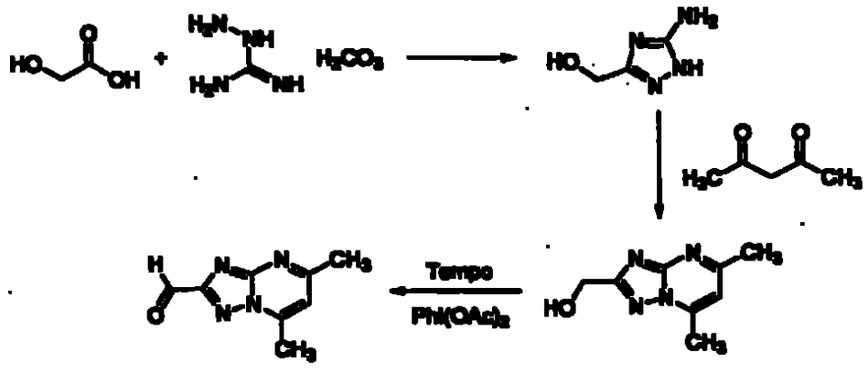
(31) (32) (29)

Los compuestos de fórmula (31) están disponibles en el mercado o pueden prepararse por métodos conocidos por los especialistas habituales en la técnica.

Los compuestos de fórmula (32) en la que M es un metal adecuado están disponibles en el mercado o pueden prepararse fácilmente por métodos conocidos por un especialista habitual en la técnica. Por ejemplo, el compuesto de fórmula (32) en la que M es -MgBr puede prepararse a partir de bromuro de vinilo y un precursor de magnesio adecuado, tal como metal magnesio o magnesio Rieke activado. Estas reacciones pueden realizarse en un disolvente prótico tal como éter dietílico, metil terc-butil éter, o tetrahidrofurano y a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 25°C. Los compuestos de fórmula (32) en la que M es Li pueden prepararse a partir de un haluro adecuado, tal como un bromuro o yoduro y un reactivo de alquil litio adecuado, tal como butil litio o terc-butil litio. Estas reacciones pueden realizarse en un disolvente prótico tal como éter dietílico, metil terc-butil éter, o tetrahidrofurano y a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 25°C.

Los compuestos de fórmula (24), tales como (24a) mostrados más adelante, están disponibles en el mercado o pueden prepararse usando métodos conocidos por un especialista habitual en la técnica. Por ejemplo, el compuesto de fórmula (24a) se preparó por reacción de ácido glicólico con bicarbonato de aminoguanidina para producir (5amino-1H-1,2,4-triazot-3-il)metanol. Después se permitió que el producto reaccionara con 2,4-pentanodiona para proporcionar (5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-

il)metanol, que después se oxidó usando 2,2,6,6-tetrametil-1-piperidiniloxi y diacetato de yodobenceno para dar 5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído.



(IXa)

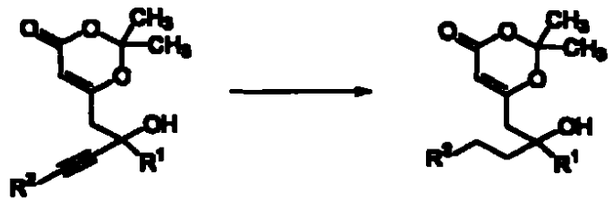
Los compuestos de fórmula (11), en la que R^1 es como se ha definido anteriormente y R^2 es un arilo C_6-C_{10} opcionalmente sustituido o un heterociclo de 4 a 10 miembros opcionalmente sustituido, pueden prepararse a partir de compuestos de fórmula (17) por reacción con una base adecuada en un disolvente adecuado.



(17) (11)

Tales reacciones pueden realizarse usando una base adecuada en un disolvente adecuado. Las bases adecuadas incluyen, pero sin limitación, carbonato potásico, carbonato sódico, bicarbonato potásico, bicarbonato sódico, hidróxido potásico e hidróxido sódico. Los disolventes que pueden usarse incluyen, pero sin limitación, alcohol metílico, alcohol etílico, alcohol iso-propílico, alcohol n-propílico, acetonitrilo y DMF, o una mezcla de los mismos. Además, si es necesario puede usarse agua como codisolvente. Estas reacciones pueden realizarse a una temperatura de aproximadamente 0°C a aproximadamente 150°C. La elección particular de una base o bases, disolvente o combinación de disolventes y de la temperatura de reacción dependerá del material de partida particular a usar y tales elecciones están dentro del conocimiento de un especialista habitual en la técnica y pueden realizarse sin una experimentación excesiva.

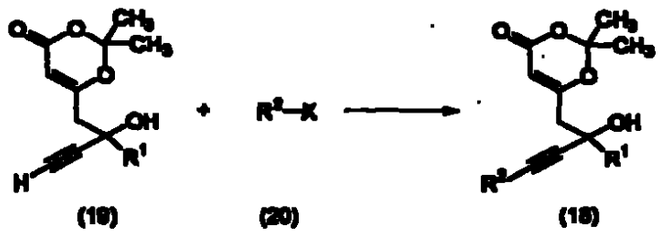
Los compuestos de fórmula (17), en la que R^1 es como se ha definido anteriormente en este documento y R^2 es un arilo C_6-C_{10} opcionalmente sustituido o un heterociclo de 4 a 10 miembros opcionalmente sustituido, pueden prepararse a partir de compuestos de fórmula (18) por reacción con un agente reductor en presencia de un catalizador.



(18) (17)

Estas reacciones típicamente se realizan en presencia de un catalizador metálico, tal como un catalizador de paladio, un agente reductor, tal como hidrógeno y en un disolvente. Además, estas reacciones pueden realizarse a una temperatura de aproximadamente 25°C a aproximadamente 150°C dependiendo del sustrato, el catalizador, el agente reductor y el disolvente. Los catalizadores útiles en tales reacciones incluyen, pero sin limitación, Pd sobre carbono (5% p/p y 10% p/p, por ejemplo), Pt sobre carbono (5% p/p y 10% p/p, por ejemplo), hidróxido de paladio y níquel Raney. Los agentes reductores adecuados que pueden usarse incluyen, pero sin limitación, hidrógeno y formiato amónico. Cuando se usa hidrógeno como el agente reductor, es ventajoso presurizar el recipiente de reacción con al menos una atmósfera de gas hidrógeno. Los disolventes que pueden usarse incluyen, pero sin limitación, disolventes próticos tales como alcohol metílico y etílico y disolventes apróticos tales como acetonitrilo, DMF, acetato de etilo, acetona, cloroformo y diclorometano. La elección particular de un catalizador, agente reductor, disolvente y de la temperatura dependerán del sustrato particular a usar y tales elecciones están dentro del conocimiento de un especialista habitual en la técnica y pueden realizarse sin una experimentación excesiva.

Los compuestos de fórmula (18), en la que R^1 es como se ha definido anteriormente en este documento y R^2 es un arilo C_6-C_{10} opcionalmente sustituido o un heterociclo de 4 a 10 miembros opcionalmente sustituido, pueden prepararse a partir de compuestos de fórmula (19) por reacción con un compuesto de fórmula (20), en la que R^2 es un arilo C_6-C_{10} opcionalmente sustituido o un heterociclo de 4 a 10 miembros opcionalmente sustituido y X es un halógeno (tal como bromo o yodo) o $-OSO_2CF_3$, en presencia de un catalizador adecuado.

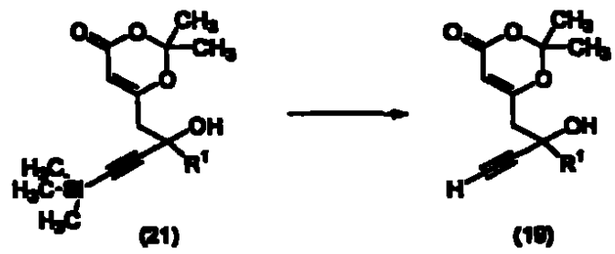


(19) (20) (18)

Estas reacciones pueden realizarse usando un compuesto de fórmula (19), un compuesto de fórmula (20), un catalizador adecuado y un compuesto de cobre adecuado (tal como yoduro de cobre (I)). Estas reacciones además se realizan en presencia de una base, tal como diisopropil amina y en un disolvente, tal como dimetilformamida (DMF). Estas reacciones pueden realizarse a una temperatura de 25°C a 150°C, dependiendo de los sustratos particulares, el catalizador y los disolventes. Los catalizadores adecuados incluyen, pero sin limitación, $PdCl_2(PPh_3)_2$, $PdCl_2$ y $Pd(PPh_3)_4$. Las bases adecuadas incluyen, pero sin limitación, trietilamina, dietilamina y dietilisopropil amina. Los disolventes que pueden usarse incluyen, pero sin limitación, acetonitrilo, dimetilformamida (DMF), acetato de etilo, 1,2-dicloroetano y cloroformo. La elección particular del catalizador de paladio, de la base, del disolvente y de la temperatura dependerán de los sustratos particulares a usar y tales elecciones están dentro del conocimiento de un especialista habitual en la técnica y pueden realizarse sin una experimentación excesiva.

Los compuestos de fórmula (20), en la que R^2 es un arilo C_6-C_{10} opcionalmente sustituido o un heterociclo de 4 a 10 miembros opcionalmente sustituido y X es un halógeno (tal como bromo o yodo) o $-OSO_2CF_3$, están disponibles en el mercado o pueden prepararse usando métodos conocidos por los especialistas habituales en la técnica.

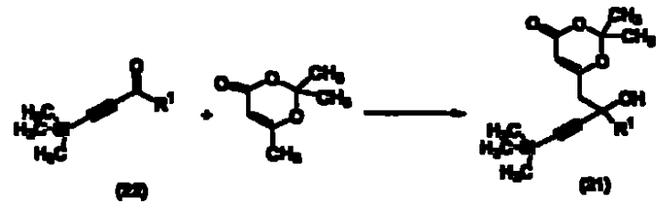
Los compuestos de fórmula (19), en la que R^1 es como se ha definido anteriormente en este documento, pueden prepararse a partir de compuestos de fórmula (21), en la que R^1 es como se ha definido anteriormente en este documento, con un reactivo o combinación de reactivos adecuados que escindan el grupo sililo en el compuesto (21).



(21) (19)

Los reactivos o combinación de reactivos adecuados que escinden el grupo sililo en el compuesto de fórmula (21) incluyen, pero sin limitación, bases fuertes, tales como hidróxido sódico e hidróxido potásico y el ion flúor (F). Las fuentes de flúor adecuadas incluyen, pero sin limitación, sales de fluoruro de amonio tales como fluoruro de tetrabutil amonio. Estas reacciones pueden realizarse en un disolvente o mezcla de disolventes que no interfieran con la reacción química deseada. Los disolventes adecuados incluyen, pero sin limitación, acetato de etilo, acetato de isobutilo, acetato de isopropilo, acetato de n-butilo, metil isobutil cetona, dimetoxietano, éter diisopropílico, clorobenceno, dimetil formamida, dimetil acetamida, propionitrilo, butironitrilo, alcohol t-amílico, ácido acético, éter dietílico, metil-t-butil éter, éter difenílico, metilfenil éter, tetrahidrofurano, 2-metiltetrahidrofurano, 1,4-dioxano, pentano, hexano, heptano, metanol, etanol, 1-propanol, 2-propanol, t-butanol, nbutanol, 2-butanol, diclorometano, cloroformo, 1,2-dicloroetano, acetonitrilo, benzonitrilo, acetona, 2-butanona, benceno, tolueno, anisol, xilenos y piridina, o cualquier mezcla de los disolventes anteriores. Adicionalmente, puede usarse agua como co-disolvente si no interfiere con la transformación deseada. Finalmente, tales reacciones pueden realizarse a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 100°C, o en el intervalo de aproximadamente 0°C a aproximadamente 75°C, o en el intervalo de aproximadamente 0°C a aproximadamente 50°C, o en el intervalo de 25°C a aproximadamente 50°C. La elección particular del reactivo o combinación de reactivos de desprotección, del disolvente y de la temperatura está dentro del conocimiento de un especialista habitual en la técnica y puede realizarse sin una experimentación excesiva.

Los compuestos de fórmula (21), en la que R^1 es como se ha definido anteriormente en este documento, pueden prepararse a partir de compuestos de fórmula (22), en la que R^1 es como se ha definido anteriormente en este documento, por reacción con 2,2,6trimetil-[1,3]mioxin-4-ona.

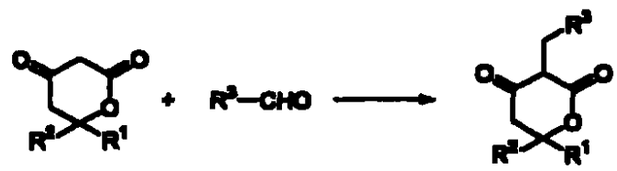


(22) (21)

Estas reacciones pueden realizarse en presencia de una base que desprotone a la 2,2,6trimetil-[1,3]-dioxin-4-ona. Las bases adecuadas incluyen, pero sin limitación, diisopropil amida de litio, terc-butil litio y n-butil litio. Bases tales como diisopropil amida de litio pueden generarse in situ por reacción con diisopropil amina y un reactivo de alquil litio, tal como terc-butil litio o nbutil litio y pueden usarse sin aislamiento o purificación adicional. Estas reacciones también pueden realizarse en un disolvente que no interfiera con la reacción química deseada. Los disolventes adecuados incluyen, pero sin limitación, disolventes apróticos tales como éter dietílico, metil terc-butil éter y tetrahidrofurano. Por último, estas reacciones pueden realizarse a una temperatura en el intervalo de aproximadamente -78°C a aproximadamente la temperatura ambiente, o en el intervalo de aproximadamente -78°C a aproximadamente 0°C, o en el intervalo de aproximadamente -78°C a aproximadamente -30°C. La elección de una base particular, del disolvente y de la temperatura están dentro del conocimiento de un especialista habitual en la técnica y tales elecciones pueden realizarse sin una experimentación excesiva.

Los compuestos de fórmula (22), en la que R^1 es como se ha definido anteriormente en este documento, están disponibles en el mercado o pueden prepararse usando métodos conocidos por los especialistas habituales en la técnica, tales como los encontrados en *Journal of Organic Chemistry*, 1984, 4786-4800.

Los compuestos de fórmula (4) pueden prepararse en forma estereoisoméricamente enriquecida por reacción de un compuesto de fórmula (11), que está estereoisoméricamente enriquecido, con un compuesto de fórmula (12).

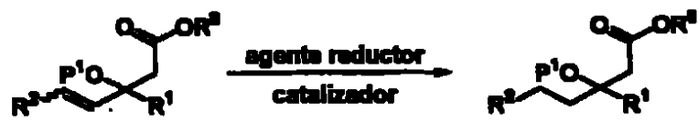


(11) (12) (4)

Generalmente, estas reacciones se realizan en presencia de un agente reductor

tal como una fuente de boro o hidrógeno en presencia de un catalizador adecuado. Las fuentes de borano adecuadas incluyen, pero sin limitación, complejo de borano-trimetilamina, complejo de borano-dimetilamina, complejo de borano t-butil amina y complejo de borano-piridina. Los catalizadores adecuados para uso en presencia de un agente reductor tal como hidrógeno incluyen, pero sin limitación, níquel, paladio, rodio y rutenio. Además, tales reacción se realizan en un disolvente o mezcla de disolventes que no interfiera con la reacción química deseada. Además, los disolventes apropiados incluyen los conocidos por los especialistas en la técnica por ser compatibles con las condiciones de reacción e incluyen ésteres de alquilo y ésteres de arilo, éteres de alquilo, heterociclilo y arilo, hidrocarburos, alcoholes de alquilo y arilo, compuestos de alquilo y arilo hidrogenados, nitrilos de alquilo o arilo, cetonas de alquilo y arilo y disolventes heterocíclicos no próticos. Por ejemplo, los disolventes adecuados incluyen, pero sin limitación, acetato de etilo, acetato de isobutilo, acetato de isopropilo, acetato de n-butilo, metil isobutil cetona, dimetoxietano, éter diisopropílico, clorobenceno, dimetil formamida, dimetil acetamida, propionitrilo, butironitrilo, alcohol t-amílico, ácido acético, éter dietílico, metil-t-butil éter, éter difenílico, metilfenil éter, tetrahidrofurano, 2-metiltetrahidrofurano, 1,4-dioxano, pentano, hexano, heptano, metanol, etanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, diclorometano, cloroformo, 1,2-dicloroetano, acetonitrilo, benzonitrilo, benceno, tolueno, anisol, xilenos y piridina, o cualquier mezcla de los disolventes anteriores. Adicionalmente puede usarse agua como co-disolvente si no interfiere con la transformación deseada. Finalmente, tales reacciones pueden realizarse a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 75°C, preferiblemente en el intervalo de aproximadamente 0°C a aproximadamente 32°C, más preferiblemente a la temperatura ambiente. La elección de un agente reductor, disolvente y temperatura particular dependerá de diversos factores incluyendo, aunque sin limitación, la identidad de los reactivos particulares y los grupos funcionales presentes en tales reactivos. Tales elecciones están dentro del conocimiento de un especialista en la técnica y pueden realizarse sin excesiva experimentación.

Los compuestos de fórmula (9), en la que R^1, R^2 y R^8 son como se han definido anteriormente en este documento, pueden prepararse a partir de compuestos de fórmula (8), en la que R^1, R^2 y R^8 son como se han definido anteriormente en este documento, con un agente reductor en presencia de un catalizador.

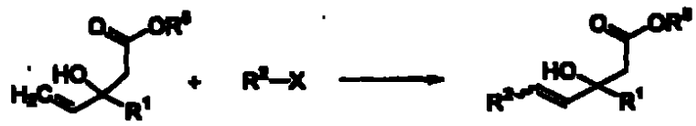


(8) (9)

Los agentes reductores adecuados para esta reacción son aquellos que son capaces de transferir hidrógeno (H_2) al alqueno para producir el alcano deseado, compuesto (9). Los agentes reductores adecuados incluyen, pero sin limitación gas hidrógeno, ácido fórmico y sales de ácido fórmico tales como formiato amónico. Cuando se usa gas hidrógeno como el agente reductor, el recipiente de reacción normalmente se presuriza con gas hidrógeno. Los catalizadores adecuados para esta reacción incluyen los que son capaces de reducir el alqueno en el compuesto (8) para producir el alcano (9) en presencia de los agentes reductores adecuados descritos anteriormente. Los catalizadores adecuados incluyen, pero sin limitación, Pd (0), Pt (0) y Ni (0). Estos catalizadores pueden prepararse in situ a partir de pre-catalizadores adecuados que pueden ser más auto estables. Los pre-catalizadores adecuados incluyen, pero sin limitación, paladio sobre carbono (5% p/p y 10% p/p, por ejemplo), $PdCl_2$, $Pd(OH)_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $PtCl_2$, $Pt(OH)_2$ y níquel Raney. Además, estas reacciones pueden realizarse en un disolvente o mezcla de disolventes que no interfieran con la reacción química deseada. Los disolventes adecuados incluyen, pero sin limitación, ésteres de alquilo y ésteres de arilo, éteres de alquilo, heterociclilo y arilo, hidrocarburos, alcoholes de alquilo y arilo, compuestos de alquilo y arilo halogenados, nitrilos de alquilo o arilo, cetonas de alquilo y arilo y disolventes heterocíclicos no próticos. Por ejemplo, los disolventes adecuados incluyen, pero sin limitación, acetato de etilo, acetato de isobutilo, acetato de isopropilo, acetato de n-butilo, metil isobutil cetona, dimetoxietano, diisopropil éter, clorobenceno, dimetil formamida, dimetil acetamida, propionitrilo, butironitrilo, alcohol t-amílico, ácido acético, éter dietílico, metil-t-butil éter, éter difenílico, metilfenil éter, tetrahidrofurano, 2-metiltetrahidrofurano, 1,4-dioxano, pentano, hexano, heptano, metanol, etanol, 1-propanol, 2propanol, t-butanol, n-butanol, 2-butanol, diclorometano, cloroformo, 1,2-dicloroetano, acetonitrilo, benzonitrilo, acetona, 2-butanona, benceno, tolueno, anisol, xilenos y piridina, o cualquier mezcla de los disolventes anteriores. Adicionalmente, puede usarse agua como co-disolvente si no interfiere con la transformación deseada. Finalmente, tales reacciones pueden realizarse a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 100°C, o en el intervalo de aproximadamente 0°C a aproximadamente 75°C, o en el intervalo

de aproximadamente 0°C a aproximadamente 50°C, o en el intervalo de 25°C a aproximadamente 50°C. La elección de un agente reductor particular, del catalizador, del disolvente y de la temperatura dependerán de diversos factores incluyendo, pero sin limitación, la identidad de los reactivos y la presencia o ausencia de otros grupos funcionales. Tales elecciones están dentro del conocimiento de un especialista en la técnica y pueden realizarse sin excesiva experimentación.

Los compuestos de fórmula (8), en la que R^1, R^2 y R^8 son como se han definido anteriormente en este documento, pueden prepararse a partir de compuestos de fórmula (7),en la que R^1 y R^8 son como se han definido anteriormente en este documento, por reacción con un compuesto de fórmula (6), en la que X es un halógeno o $-OSO_2CF_3$ y R^2 es como se ha definido anteriormente en este documento, en presencia de un catalizador adecuado.



(7) (6) (8)

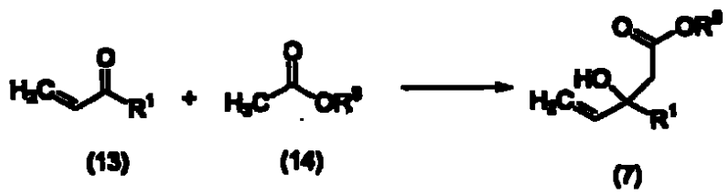
Estas reacciones pueden realizarse en presencia de un catalizador que sea química y catalíticamente competente para realizar la denominada reacción de tipo Heck. Los catalizadores adecuados incluyen especies de Pd(0), unidos o sin unir a diversos ligandos apropiados. Tales catalizadores pueden generarse in situ a partir de pre-catalizadores adecuados en presencia de un ligando apropiado. Los pre-catalizadores adecuados incluyen, pero sin limitación, $PdCl_2$, $PdCl_2(PPh_3)_2$, y $Pd(PPh_3)_4$. La cantidad de pre-catalizador usada en estas reacciones dependerá de los sustratos de reacción particulares, de la temperatura a la que se realiza la reacción y del disolvente en el que se realiza la reacción. Los catalizadores usados pueden estar en el intervalo de aproximadamente 0,01% en moles (con respecto a la cantidad del compuesto (7) o (6)) a aproximadamente 99% en moles, o en el intervalo de aproximadamente 0,01% en moles a aproximadamente 50% en moles, o en el intervalo de aproximadamente 0,01% en moles a aproximadamente 25% en moles, o en el intervalo de aproximadamente 0,01% en moles a aproximadamente 10% en moles, o en el intervalo de aproximadamente 0,01% en moles a aproximadamente 5% en moles. Estas reacciones también pueden realizarse en presencia de una base. Las bases adecuadas incluyen, pero sin limitación, bases orgánicas tales como trietilamina y acetato sódico y

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bases inorgánicas tales como carbonato sódico, bicarbonato sódico, carbonato potásico, bicarbonato potásico y carbonato de cesio. Estas reacciones pueden realizarse en un disolvente que no interfiera con la reacción química deseada. Los disolventes adecuados incluyen, pero sin limitación, acetato de etilo, acetato de isobutilo, acetato de isopropilo, nbutil acetato, metil isobutil cetona, dimetoxietano, éter diisopropílico, clorobenceno, dimetil formamida, dimetil acetamida, propionitrilo, butironitrilo, alcohol t-amílico, ácido acético, éter dietílico, metil-t-butil éter, éter difenílico, metilfenil éter, tetrahidrofurano, 2-metiltetrahidrofurano, 1,4-dioxano, pentano, hexano, heptano, metanol, etanol, 1-propanol, 2-propanol, t-butanol, nbutanol, 2-butanol, diclorometano, cloroformo, 1,2-dicloroetano, acetonitrilo, benzonitrilo, acetona, 2-butanona, benceno, tolueno, anisol, xilenos, 1-metil-2-pirrolidinona y piridina, o cualquier mezcla de los disolventes anteriores. Adicionalmente, puede usarse agua como co-disolvente si no interfiere con la transformación deseada. Finalmente, estas reacciones pueden realizarse a una temperatura en el intervalo de aproximadamente 0°C a aproximadamente 150°C, o en el intervalo de aproximadamente 25°C a aproximadamente 150°C, o en el intervalo de aproximadamente 25°C a aproximadamente 100°C. La elección particular de un catalizador, de la base, del disolvente y de la temperatura está dentro del conocimiento de un especialista habitual en la técnica y puede realizarse sin una experimentación excesiva.

Los compuestos de fórmula (6), en la que X es un halógeno o - OSO_2CF_3 y R^2 es como se ha definido anteriormente en este documento están disponibles en el mercado o pueden prepararse de acuerdo con métodos conocidos por los especialistas en la técnica.

Los compuestos de fórmula (7), en la que R^1 y R^8 son como se han definido anteriormente en este documento, pueden prepararse a partir de compuestos de fórmula (13), en la que R^1 es como se ha definido anteriormente en este documento, por reacción con un compuesto de fórmula (14), en la que R^8 es alquilo C_1-C_6.



(13) (14) (7)

Estas reacciones pueden realizarse en presencia de un compuesto adecuadamente básico que sea capaz de desprotonar el compuesto de fórmula (14). Las bases

adecuadas incluyen, pero sin limitación, hexametildisilazida de litio (LiHMDS) y diisopropil amida de litio (LDA). Además, estas reacciones pueden realizarse en presencia de un disolvente que no interfiera con la reacción química deseada. Los disolventes adecuados incluyen, pero sin limitación, dimetoxietano, éter diisopropílico, clorobenceno, éter dietílico, metil-t-butil éter, éter difenílico, metilfenil éter, tetrahidrofurano, 2-metiltetrahidrofurano, 1,4-dioxano, pentano, hexano, heptano, benceno, tolueno, anisol, xilenos y piridina, o cualquier mezcla de los disolventes anteriores. Por último, estas reacciones pueden realizarse a una temperatura en el intervalo de aproximadamente -78°C a aproximadamente 25°C, o en el intervalo de aproximadamente -78°C a aproximadamente 0°C. La elección particular de una base, del disolvente y de la temperatura está dentro del conocimiento de un especialista habitual en la técnica y puede realizarse sin una experimentación excesiva.

Los compuestos de fórmula (7), en la que R^1 es como se ha definido anteriormente en este documento y R^8 es hidrógeno, pueden prepararse en forma estereoisoméricamente enriquecida a partir de un compuesto racémico o escalénico de fórmula (7), en la que R^1 es como se ha definido anteriormente en este documento y R^8 es hidrógeno, por: a) reacción con una base quiral no racémica para producir una mezcla de sales diastereoméricas; b) separación de las sales diastereoméricas entre sí; y 3) conversión del compuesto de fórmula (7) por reacción con un compuesto ácido adecuado. Las bases quirales no racémicas adecuadas incluyen aminas quirales no racémicas. Las aminas quirales no racémicas útiles incluyen, pero sin limitación, (S)-1,2,3,4-tetrahidro-1-naftilamina, (R)-1,2,3,4-tetrahidro1-naftilamina, (S)-(-)-1-(2-naftil)etilamina, (R)-(-)-1-(2-naftil)etilamina, (1R,2S)-(-)-norefedrina, (1S,2R)-(-)-norefedrina. Estas reacciones pueden realizarse en un disolvente que no interfiera con la reacción química deseada. Los disolventes adecuados incluyen, pero sin limitación, acetato de etilo, acetato de isobutilo, acetato de isopropilo, acetato de n-butilo, metil isobutil cetona, dimetoxietano, éter diisopropílico, clorobenceno, dimetil formamida, dimetil acetamida, propionitrilo, butironitrilo, alcohol t-amílico, ácido acético, éter dietílico, metil-t-butil éter, éter difenílico, metilfenil éter, tetrahidrofurano, 2-metiltetrahidrofurano, 1,4-dioxano, pentano, hexano, heptano, metanol, etanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, diclorometano, cloroformo, 1,2-dicloroetano, acetonitrilo, benzonitrilo, acetona, 2-butanona, benceno, tolueno, anisol, xilenos y piridina, o cualquier mezcla de los disolventes anteriores. Adicionalmente puede usarse agua como co-disolvente si no interfiere con la transformación deseada. Finalmente, estas reacciones pueden realizarse a una temperatura en el intervalo de

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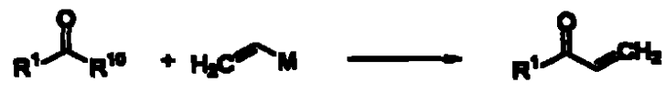
aproximadamente 0°C a aproximadamente 150°C, o en el intervalo de aproximadamente 25°C a aproximadamente 150°C, o en el intervalo de aproximadamente 25°C a aproximadamente 100°C, o a temperatura ambiente. El disolvente puede elegirse de tal forma que una de las sales diastereoméricas sea apreciablemente soluble en el disolvente mientras que la otra sal diastereomérica es apreciablemente insoluble en el disolvente. Tal diferencia en las solubilidades puede usarse para efectuar la separación de las sales diastereoméricas entre sí por la precipitación de una de las sales diastereoméricas en forma estereoisoméricamente enriquecida. Después de la precipitación de sustancialmente una sal diastereomérica, puede aumentarse la pureza estereoisomérica de la sal mediante la recristalización repetida en un disolvente o mezcla de disolventes apropiados. La conversión de una sal diastereomérica estereoisoméricamente enriquecida puede realizarse por reacción de la sal con un compuesto ácido adecuado. Los ácidos adecuados incluyen, pero sin limitación, ácidos inorgánicos (tales como ácido clorhídrico, ácido bromhídrico, ácido yodhídrico, ácido sulfúrico, ácido nítrico y ácido fosfórico) y ácidos orgánicos (tales como ácido acético, ácido fórmico y ácido cítrico).

Como alternativa, el compuesto de fórmula 7, en la que R^1 es como se ha definido anteriormente en este documento y R^8 es hidrógeno, puede obtenerse en forma estereoisoméricamente enriquecida por reacción con un alcohol quiral no racémico, para producir una mezcla de ésteres diastereoméricos. Los ésteres diastereoméricos pueden obtenerse por reacción del compuesto de fórmula (7) con el alcohol deseado en presencia de un agente de activación o mezcla de agentes de activación adecuados. Los agentes de activación adecuados incluyen, pero sin limitación, carbodiimidas (tales como dietilcarbodiimida), diazodicarboxilato de dietilo, cloruro de tionilo, fosgeno y trifosgeno. La reacción del alcohol quiral no racémico con el compuesto activado de fórmula (7) puede realizarse en presencia de una base adecuada. Las bases adecuadas incluyen, pero sin limitación, bases orgánicas tales como trietilamina, dietilisopropilamina, piridina y 4,4-N,N-dimetilaminopiridina. Una vez obtenido, los compuestos de éster diastereoméricos de fórmula (7) pueden separarse entre sí usando métodos conocidos por los especialistas en la técnica, incluyendo, pero sin limitación, cromatografía y cristalización fraccionada. La elección de un alcohol quiral no racémico y las condiciones para la separación de la mezcla de ésteres diastereoméricos está dentro del conocimiento de un especialista habitual en la técnica y puede realizarse sin una experimentación excesiva.

Los compuestos de fórmula (14) están disponibles en el mercado o pueden pre-

pararse usando métodos conocidos por los especialistas habituales en la técnica.

Los compuestos de fórmula (13), en la que R^1 es como se ha definido anteriormente en este documento, pueden prepararse a partir de compuestos de fórmula (15), en la que R^1 es como se ha definido anteriormente en este documento y R^{10} es un grupo saliente adecuado, con un compuesto de fórmula (16), en la que M es un grupo capaz de transferir el grupo vinilo del compuesto (16) al compuesto de fórmula (15).



(15) (16) (13)

Estas reacciones pueden realizarse con un compuesto de fórmula (16), en la que M es un derivado de magnesio, tal como cloruro de magnesio o bromuro de magnesio, con un compuesto de fórmula (15), en la que R^{10} es un grupo $-N(OCH_3)CH_3$. Estas reacciones pueden realizarse en un disolvente aprótico que no interfiera con la reacción química deseada. Los disolventes adecuados incluyen, pero sin limitación, éter dietílico, terc-butil metil éter, éter diisopropílico y tetrahidrofurano. Además, tales reacciones pueden realizarse en el intervalo de aproximadamente -78°C a aproximadamente 25°C, o en el intervalo de aproximadamente -78°C a aproximadamente 0°C. La elección de un disolvente y temperatura particulares está dentro del conocimiento de un especialista habitual en la técnica y puede realizarse sin una experimentación excesiva.

Como alternativa, los compuestos de fórmula (13) pueden prepararse por reacción de compuestos de fórmula (15), en la que R^1 es como se ha definido anteriormente en este documento y R^{10} es un grupo saliente adecuado, tal como cloruro, por reacción con un compuesto de fórmula (16), en la que M es un grupo adecuado tal como $-Si(CH_3)_3$. Los compuestos de fórmula (15) en la que R^{10} es un grupo saliente adecuado, tal como cloro, pueden prepararse a partir de compuestos de fórmula (15) en la que R^{10} es -OH por reacción con un agente de activación. Los agentes de activación adecuados incluyen, pero sin limitación, cloruro de oxalilo, cloruro de tionilo, fosgeno y trifosgeno. Estas reacciones pueden realizarse en un disolvente que no interfiera con la reacción química deseada. Los disolventes adecuados incluyen, pero sin limitación, disolventes apróticos tales como diclorometano, cloroformo, 1,2-dicloroetano y N,N-dimetilformamida (DMF). La reacción del compuesto de fórmula (15) en la que R^{10} es un grupo saliente adecuado, tal como cloruro, con el compuesto de fórmula (16), en la que M es un grupo adecuado tal como $-Si(CH_3)_3$, puede realizarse en un disolvente que

no interfiera con la reacción química deseada. Los disolventes adecuados incluyen, pero sin limitación, disolventes apróticos tales como diclorometano, cloroformo, 1,2-dicloroetano y N,N-dimetil-formamida (DMF). Además, tales reacciones pueden realizarse en presencia de un ácido de Lewis para ayudar en el desplazamiento del grupo saliente por el grupo vinilo. Los ácidos de Lewis adecuados incluyen, pero sin limitación, cloruro de aluminio, cloruro de estaño (IV), cloruro de estaño (II) y tetracloruro de titanio. La cantidad requerida de un ácido de Lewis particular puede variar de aproximadamente 1% en moles a aproximadamente 125% en moles (basado en la pareja de reacción de vinil silano) y dependerá de la identidad del ácido de Lewis usado, la identidad de las parejas de reacción, del disolvente usado y de la temperatura a la que se realiza la reacción. Finalmente, estas reacciones pueden realizarse a una temperatura en el intervalo de aproximadamente -78°C a aproximadamente 100°C, o en el intervalo de aproximadamente -78°C a aproximadamente 25°C, o preferiblemente en el intervalo de aproximadamente -78°C a aproximadamente 0°C.

Los compuestos de fórmula (15) en la que R^{10} es un grupo $-N(OCH_3)CH_3$ pueden prepararse a partir de compuestos de fórmula (15) en la que R^{10} es un grupo saliente adecuado, tal como -Cl, por reacción con N,Odimetilhidroxilamina. Estas reacciones se realizan en presencia de una base adecuada. Las bases adecuadas incluyen, pero sin limitación, bases orgánicas (tales como trietilamina, piridina y N,N-4-dimetilaminopiridina) y bases inorgánicas (tales como carbonato sódico, bicarbonato sódico, carbonato potásico, bicarbonato potásico y carbonato de cesio). Además, estas reacciones pueden realizarse en un disolvente que no interfiera con la reacción química deseada. Los disolventes adecuados incluyen, pero sin limitación, acetato de etilo, acetato de isobutilo, acetato de isopropilo, acetato de n-butilo, metil isobutil cetona, dimetoxietano, diisopropil éter, clorobenceno, dimetil formamida, dimetil acetamida, propionitrilo, butironitrilo, ácido acético, éter dietílico, metil-t-butil éter, éter difenílico, metilfenil éter, tetrahidrofurano, 2-metiltetrahidrofurano, 1,4-dioxano, pentano, hexano, heptano, diclorometano, cloroformo, 1,2-dicloroetano, acetonitrilo, benzonitrilo, acetona, 2-butanona, benceno, tolueno, anisol, xilenos y piridina, o cualquier mezcla de los disolventes anteriores. Adicionalmente puede usarse agua como co-disolvente si no interfiere con la transformación deseada.

Los compuestos de fórmula (15) en la que R^{10} es -OH están disponibles en el mercado o pueden prepararse por métodos conocidos por un especialista habitual en la técnica.

Los compuestos de fórmula (16) en la que M es un derivado de magnesio, tal

como -MgBr o -MgCl, están disponibles en el mercado o pueden prepararse a partir de compuestos de fórmula (16) en la que M es un halógeno, preferiblemente bromo o yodo, por reacción con un reactivo de magnesio adecuado. Los reactivos de magnesio adecuados incluyen, pero sin limitación, magnesio (0) y magnesio Rieke. Normalmente, los reactivos se forman in situ en la mezcla de reacción y se usan sin aislamiento o purificación adicionales.

Los compuestos de fórmula (16) en la que M es $-Si(CH_3)_3$ están disponibles en el mercado o pueden prepararse a partir de compuestos de fórmula (16) es un derivado de magnesio, tal como -MgBr o -MgCl por reacción con $XSi(CH_3)_3$, donde X es cloro, bromo o yodo. Normalmente, estos compuestos se forman in situ en la mezcla de reacción y se usan sin purificación adicional ni aislamiento.

Se entiende que los siguientes ejemplos ilustran sólo realizaciones particulares de la presente invención y no se pretende que limiten el alcance de la invención en forma alguna.

A menos que se indique otra cosa, todos los números que expresan cantidades de ingredientes, propiedades tales como el peso molecular, condiciones de reacción y demás en la memoria descriptiva y en las reivindicaciones, se entiende en todos los casos que se modifica por el término "aproximadamente". Por consiguiente, a menos que se indique otra cosa, los parámetros numéricos indicados en la siguiente descripción y en las reivindicaciones adjuntas son aproximaciones que pueden variar dependiendo de las propiedades que se deseen obtener por la presente invención. Como mínimo, y sin intención de limitar la aplicación de la doctrina de equivalentes al alcance de las reivindicaciones, cada parámetro numérico debe interpretarse al menos a la luz del número de dígitos significativos presentados y aplicando técnicas normales.

Ejemplos

En los ejemplos mostrados a continuación, a menos que se indique otra cosa, todas las temperaturas en la siguiente descripción están en grados centígrados (°C) y todas las partes y porcentajes son en peso, a menos que se indique otra cosa.

Diversos materiales de partida y otros reactivos se adquirieron de suministradores comerciales tales como Aldrich Chemical Company o Lancaster Synthesis Ltd. y se usaron sin purificación adicional, a menos que indique otra cosa.

Las reacciones mostradas a continuación se realizaron bajo una presión positiva de nitrógeno, argón o con un tubo de secado, a temperatura ambiente (a menos que se indique otra cosa), en disolventes anhidros. Se realizó una cromatografía de capa

fina analítica en placas de gel de sílice con soporte de vidrio 60°F 254 (Analtech (0,25 mm)) y la elución se realizó con las relaciones de disolventes apropiadas (v/v). Las reacciones se ensayaron por cromatografía de líquidos de alta presión (HPLC) o cromatografía en capa fina (TLC) y se terminaron cuando se estima el agotamiento del material de partida. Las placas de TLC se visualizaron por UV, tinción con ácido fosfomolíbdico, o tinción con yodo.

Los espectros de ^{1}H-RMN se registraron sobre un instrumento Bruker que funcionaba a 300 MHz o 400 MHz y los espectros de ^{13}C RMN se registraron a 75 MHz. Los espectros de RMN se obtuvieron como soluciones en DMSO-d_6 o $CDCl_3$ (datos proporcionados en ppm), usando cloroformo como el patrón de referencia (7,25 ppm y 77,00 ppm) o DMSO-d_6 (2,50 ppm y 39,52 ppm). Se usaron otros disolventes para RMN cuando fue necesario. Cuando se informan múltiples picos, se usan las siguientes abreviaturas: s = singlete, d = doblete, t = triplete, m = multiplete, a = ancho, dd = doblete de dobletes, dt = doblete de tripletes. Las constantes de acoplamiento, cuando aparecen, se indican en Hertz.

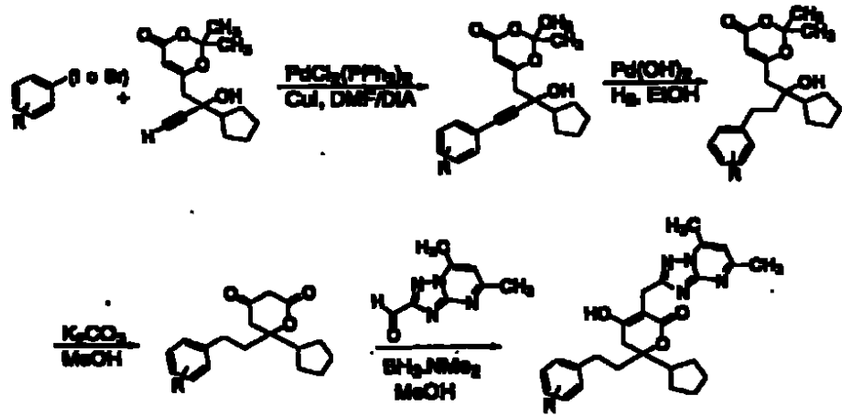
Los espectros infrarrojos se registraron sobre un espectrómetro Perkin-Elmer PT-IR como aceites puros, como gránulos de KBr o como soluciones en $CDCl_3$, y los datos se proporcionaron en números onda (cm^{-1}). Los espectros de masas se obtuvieron usando LC/MS o APCI. Todos los puntos de fusión están sin corregir.

Todos los productos finales tuvieron una pureza mayor de 95% (por HPLC a longitudes de onda de 220nm y 254nm).

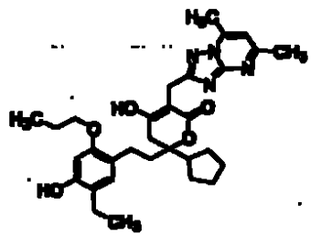
En los siguientes ejemplos y preparaciones, "Et" se refiere a etilo, "Ac" se refiere a acetilo, "Me" se refiere a metilo, "Ph" se refiere a fenilo, "$(PhO)_2POCl$" se refiere a clorodifenilfosfato, "HCl" se refiere a ácido clorhídrico, "EtOAc" se refiere a acetato de etilo, "Na_2CO_3" se refiere a carbonato sódico, "NaOH" se refiere a hidróxido sódico, "NaCl" se refiere a cloruro sódico, "NEt_3" se refiere a trietilamina , "THF" se refiere a tetrahidrofurano, "DIC" se refiere a diisopropilcarbodiimida, "HOBt" se refiere a hidroxi benzotriazol, "H_2O" se refiere a agua, "$NaHCO_3$" se refiere a hidrogenocarbonato sódico, "K_2CO3" se refiere a carbonato potásico, "MeOH" se refiere a metanol, "i-PrOAc" se refiere a acetato de isopropilo, "$MgSO_4$" se refiere a sulfato de magnesio, "DMSO" se refiere a dimetilsulfóxido, "AcCl" se refiere a cloruro de acetilo, "CH_2Cl_2" se refiere a cloruro de metileno, "MTBE" se refiere a metil t-butil éter, "DMF" se refiere a dimetil formamida, "$SOCl_2$" se refiere a cloruro de tionilo, "H_3PO_4" se refiere a ácido fosfórico, "CH_3SO_3H" se refiere a ácido metanosulfónico, " Ac_2O" se refiere a anhídrido acético, "CH_3CN" se refiere a acetonitrilo, "KOH" se refiere a hidróxido potásico, "CDI" se refiere

a carbonil diimidazol, "DABCO" se refiere a 1,4-diazabiciclo[2.2.2]octano, "IPE" se refiere a éter isopropílico, "MTBE" se refiere a metil terc-butil éter, "Et_2O" se refiere a éter dietílico, "Na_2SO_4 se refiere a sulfato sódico, "NBS" se refiere a N-bromosuccinimida, "TEA" se refiere a trietilamina, "DCM" se refiere a diclorometano, "TBAB" se refiere a bromuro de tetrabutilamonio, "HMPA" se refiere a hexametilfosforamida, "NMP" se refiere a 1-metil-2-pirrolidinona, "DMAC" se refiere a N,N-dimetilacetamida, "h" se refiere a horas, "min" se refiere a minutos, "mol" se refiere a moles y "ta" se refiere a temperatura ambiente.

Esquema 1: Ruta de Sonogashira



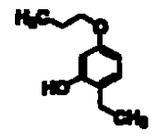
Ejemplo A(1): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2-(5-etil-4-hidroxi-2-propoxifenil)etil-hidroxi-5,6-dihidro-2H-piran-2-ona



Se añadió 5,7-dimetil-[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído (0,24 g, 1,4 mmol, de la etapa 8 mostrada a continuación) a una solución de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]dihidropiran-2,4-diona (0,45 g, 1,2 mmol, de la etapa 5 mostrada a continuación) en MeOH (15 ml). La mezcla de reacción se agitó durante 15 minutos y después se trató con complejo de borano-diemtilamina (100 mg, 1,7 mmol).

Después de 15 horas la mezcla de reacción se filtró a través de una frita de vidrio lavando con MeOH. El filtrado se concentró para dar un aceite amarillo. La purificación por HPLC preparativa dio el producto en forma de un polvo blanco(230 mg, 38%). ^{1}H RMN (400MHz, DMSO-d_6): δ 0,84 (t, J = 7,3 Hz, 3 H), 0,92 (t, J = 7,6 Hz, 3 H), 1,32-1,69 (m, 10 H), 1,82 (m, 1H), 1,96 (m, 1H), 2,28-2,47 (m,.11H), 2,49 (d, J = 17,5 Hz, 1H), 2,67(d, J = 17,5 Hz, 1H), 3,61-3,73 (m, 4 H), 6,26 (s, 1H), 6,63 (s, 1H), 6,95 (s, 1H), 8,87 (s, 1H), 10,72 (s, 1H). Análisis calculado para $C_{31}H_{40}N_4O_5$: C, 67,86; H, 7,25; N, 10,21, Encontrado: C. 67,69; H, 7,40; N, 10,04,

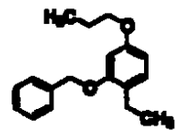
Etapa 1: 2-etil-5-propoxi-fenol



Se añadieron carbonato potásico (54 g, 0,39 mol) seguido de 1-yodopropano (11,5 ml, 0,12 mol) a una solución de 2',4'-dihidroxiacetofenona (20 g, 0,13 mol) en DMF (150 ml). La mezcla se agitó durante 5 horas y después se repartió entre H_2O y EtOAc. La capa orgánica se lavó con $NaHCO_3$ saturado y salmuera, se secó sobre Na_2SO_4 y se concentró hasta un aceite transparente (21,1 g, 91%).

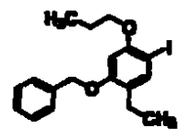
El aceite se disolvió en MeOH (100 ml), se trató con Pd al 10%/C. (6 g, tipo Degussa) y se agitó en un globo de H_2 durante 24 horas. La mezcla de reacción se filtró a través de una capa de celite lavando con EtOAc. El filtrado se concentró y se purificó por cromatografía en columna ultrarrápida (EtOAc al 0%-20% en hexanos) para dar un aceite naranja (15 g, 93%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,01 (t, J = 7,3 Hz, 3 H), 1,20 (t, J = 7,6 Hz, 3 H), 1,78 (m, 2 H), 2,56 (q, J = 7,6 Hz, 2 H), 3,86 (t, J = 6,8 Hz, 2 H), 4,90 (s, 1H), 6,37 (d, J = 2,5 Hz, 1H), 6,44 (dd, J = 8,1, 2,5 Hz, 1H), 7,01 (d, J = 8,3 Hz, 1H).

Etapa 2: 2-benciloxi-1-etil-4-propoxi-benceno



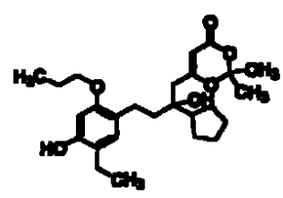
Se añadieron carbonato potásico (17,8 g, 0,13 mol) seguido de bromuro de bencilo (5,12 ml, 42,9 mmol) a una solución de 2-etil-5-propoxi-fenol (7,74 g, 42,9 mmol) en DMF (60 ml). La mezcla se agitó a 45°C for 15 horas y después se repartió entre H_2O y EtOAc. La capa orgánica se lavó con HCl 1 N y salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un aceite de color pardo. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-20% en hexanos) dio el producto en forma de un aceite transparente (6,19,55%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,02 (t, J = 7,6 Hz, 3 H), 1,19 (t, J = 7,6 Hz, 3 H), 1,78 (q, J = 7,6 Hz, 2 H), 2,63 (q, J = 7,6 Hz, 2 H), 3,88 (t, J = 6,6 Hz, 2 H),5,05 (s, 2 H), 6,44 (dd, J = 8,1, 2,3 Hz. 1H), 6,51 (dd, J = 2,3 Hz, 1H), 7,05 (d, J = 8,3 Hz, 1H), 7,31 (m, 1H), 7,38 (m, 2 H), 7,44 (m, 2 H).

Etapa 3: 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno



Una solución de yodo (2,829, 11,1 mmol) disuelto en $CHCl_3$ (80 ml) se añadió gota a gota a una mezcla agitada de 2-benciloxi-1-etil-4-propoxi-benceno (39, 11,1 mmol) y trifluoroacetato de plata (2,459, 11,1 mmol) en $CHCl_3$ (20 ml). Después de completarse la adición, la mezcla de reacción se agitó durante 1 hora. La mezcla se filtró a través de una capa de celite lavando con CH_2Cl_2. El filtrado se lavó con $Na_2S_2O_3$ saturado y salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un sólido amarillo pálido (4,04 g, 92%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,07 (t, J = 7,3 Hz, 3 H), 1,17 (t, J = 7,6 Hz. 3 H), 1,81 (m, 2 H), 2,59 (q, J = 7,6 Hz, 2 H), 3,90 (t, J = 6,3 Hz, 2 H),5,05 (s, 2 H), 6,43 (s, 1H), 7,31-7,45 (m,5 H), 7,49 (s, 1H).

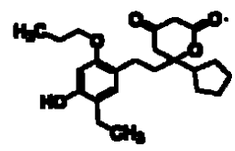
Etapa 4: 6-[2-ciclopentil-4-(5-etil-4-hidroxi-2-propoxi-fenil)-2-hidroxi-butil]-2,2-dimetil[1,3]dioxin-4-ona



Una mezcla de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno (4,0 g, 10,1 mmol), 6-(2ciclopentil-2-hidroxibut-3-inil)-2,2-dimetil-4H-1,3-dioxin-4-ona (2,42 g, 19,2 mmol, de la etapa 11 mostrada a continuación), $PdCl_2(PPh_3)_2$ (0,26 g, 4% en moles) y CuI (53 mg, 3% en moles). en diisopropilamina (12 ml) y DMF (12 ml) se calentó a 90°C durante 90 min. La mezcla de reacción se enfrió a temperatura ambiente y se repartió entre HCl 1 N y EtOAc. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un aceite negro. La cromatografía en columna ultrarrápida (EtOAc al 0%-40% en hexanos) dio un aceite de color pardo.

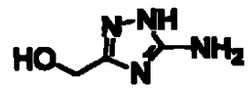
El aceite se disolvió en EtOH (30 ml) y se trató con $Pd(OH)_2$ (1g, 20% en peso, tipo Degussa). La mezcla se agitó en un globo de hidrógeno durante 4 horas. La mezcla de reacción se filtró a través de una capa de celite lavando con EtOAc. El filtrado se concentró hasta dar un aceite naranja y se purificó por cromatografía en columna ultrarrápida para dar el producto en forma de un sólido amarillo (0,838, 18%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,03 (t, J = 7,3 Hz, 3 H), 1,20 (t, J = 7,6 Hz, 3 H), 1,38-1,86 (m a, 19 H), 2,10 (m, 1H), 2,44-2,65 (m, 6 H), 3,87 (t, J = 6,6 Hz, 2 H), 4,60 (s, 1H),5,36 (s, 1H), 6,35 (s, 1H), 6,83 (s, 1H).

Etapa 5: 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona



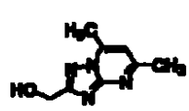
Se disolvió 6-(2-ciclopentil-4-(5-etil-4-hidroxi-2-propoxi-fenil)-2-hidroxi-butil]-2,2-dimetil[1,3]dioxin-4-ona (0,8g, 1,8 mmol) en metanol (15 ml), se trató con carbonato potásico (0,74 g,5,4 mmol) y se calentó a 45°C en una atmósfera de N_2 durante 90 minutos. La mezcla de reacción se repartió entre H_2O y IPE. La capa acuosa se acidificó con HCl 1 N y se extrajo con EtOAc. Las capas orgánicas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron para dar el producto en forma de una espuma amarilla (0,5 g, 72% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,02 (t, J = 7,3 Hz, 3 H), 1,19 (t, J = 7,6 Hz, 3 H), 1,41-1,87 (m a, 11H), 1,95 (m, 1H), 2,32 (m, 1H), 2,49-2,80 (m, 6 H), 3,41 (m, 2 H), 3,85 (m, 2 H), 4,62 (s, 1H), 6,33 (s, 1H). 6,80 (s, 1H).

Etapa 6: (5-Amino-1H-[1,2,4]triazol-3-il)-metanol



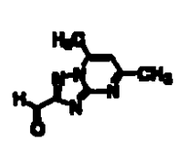
Se añadió cuidadosamente una solución de ácido glicólico (70% en agua, 70 ml, 805 mmol) a bicarbonato de aminoguanidina (55,12 g, 405 mmol). Después de que disminuyera la espumación, se añadió ácido nítrico concentrado (0,5 ml) y la reacción completa se calentó a reflujo durante 40 horas. La reacción se enfrió a 5°C durante 30 minutos y los sólidos se filtraron. Los sólidos después se trituraron con EtOH durante 1 hora. El producto después se filtró y se secó en una atmósfera de nitrógeno (40,36 g,52% de rendimiento). MS (ESI): 115 (M+H).

Etapa 7: (5,7-dimetil-[1,2,4]triazolo[1,5-a]pirimidin-2-il)-metanol



A una suspensión de (5-amino-1H-[1,2,4]triazol-3-il)-metanol (8,5 g,50 mmol) de la etapa 6 anterior en ácido acético (200 ml) se le añadió 2,4-pentanodiona (5,13 ml,50 mmol). La mezcla se calentó a reflujo durante 4 horas y después se enfrió a temperatura ambiente. El producto se aisló mediante la eliminación del disolvente por evaporación rotatoria (8,5 g, 95% de rendimiento). MS (ESI): 179 (M+H).

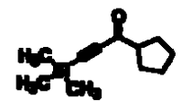
Etapa 8: 5,7-dimetil-[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído



Una suspensión de 5,7-dimetil-[1,2,4]triazolo[1,5-a]pirimidin-2-il)-metanol (0,3 g, 1,7 mmol) de la etapa 7 anterior e IBX (1,4 g,5,0 mmol) en 1,2-dicloroetano (22 ml) se agitó a 80°C durante 18 horas. La reacción se enfrió a temperatura ambiente y se diluyó con 100 ml de CH_2Cl_2. Después de que los sólidos se retiraran por filtración, el disolvente se retiró por evaporación rotatoria para dar un sólido amarillo. El sólido se purificó por cromatografía ultrarrápida para dar el producto deseado (229 mg, 77% de

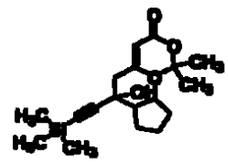
rendimiento). ^{1}H RMN ($CDCl_3$) δ: 2,72 (s, 3 H), 2,86 (s, 3 H), 6,96 (s, 1H), 10,24 (s, 1H).

Etapa 9: 1-ciclopentil-3-(trimetilsilil)prop-2-in-1-ona



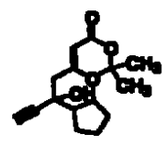
El compuesto del título se preparó como se describe en la siguiente referencia: *Journal of Organic Chemistry* **1984**, 106, 4786-4800, ^{1}H RMN ($CDCl_3$) δ: 0,24 (s, 9 H), 1,63 (m, 4 H), 1,90 (m, 4 H), 2,92 (quintuplete, 1H, J = 7,6 Hz).

Etapa 10: 6-[2-ciclopentil-2-hidroxi-4-(trimetilsilil)but-3-in-1-il]-2,2-dimetil-4H-1,3-dioxin4-ona



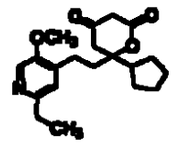
Una solución de diisopropilamina (3,85 ml, 27,5 mmol) disuelta en THF (100 ml) se enfrió a -78°C, momento en el que se añadió gota a gota BuLi (11 ml, 27,5 mmol, 2,5 M en hexanos) durante 10 minutos. Después de agitar a esta temperatura durante 5 minutos, la mezcla se calentó a temperatura ambiente durante 5 minutos, después se enfrió de nuevo a -78°C, momento en el que se añadió gota a gota 2,2,6-trimetil-[1,3]dioxin-4-ona (3,6 ml, 27,5 mmol) durante 5 minutos y después se agitó durante 30 minutos más a -78°C. A esta solución se le añadió 1-ciclopentil-3-(trimetilsilil)prop-2-in-1-ona (4,85 g, 25 mmol, de la etapa 9) durante 5 minutos. La mezcla resultante se agitó a -78°C durante 1 hora, después se calentó lentamente a -30°C y se inactivó con ácido cítrico 0,5 N. La mezcla se diluyó con éter, se lavó con $NaHCO_3$ 1 N y salmuera, se secó con $MgSO_4$ y se concentró para dar el producto bruto (9,4 g) contaminado con 2,2,6-trimetil-[1,3]dioxin-4-ona sin reaccionar. ESIMS ($M+Na^+$): 359,1,

Etapa 11: 6-(2-ciclopentil-2-hidroxibut-3-inil)-2,2-dimetil-4H-1,3-dioxin-4-ona



Una solución de 6-[2-ciclopentil-2-hidroxi-4-(trimetilsilil)but-3-in-1-il]-2,2-dimetil-4H1,3-dioxin-4-ona bruta (25 mmol) y fluoruro de cesio (7,6 g,50 mmol) disueltos en MeOH (75 ml) se agitó durante una noche. El disolvente se retiró y el residuo se diluyó con EtOAc, se lavó con ácido cítrico 0,5 N, $NaHCO_3$ 1 N y salmuera, se secó sobre $MgSO_4$ y se concentró. La purificación por cromatografía en columna ultrarrápida (EtOAc al 20%-30% en hexanos) dio el producto (3,6 g,54%). ^1H RMN (300 MHz, $CDCl_3$) δ: 1,45-1,80 (m, 8 H), 1,72 (s, 3 H), 1,74 (s, 3 H), 2,13-2,18 (m, 1H), 2,49 (s, 1H), 2,56 (s, 1H), 2,58 (s, 2 H),5,43 (s, 1H).

Ejemplo A(2): 6-ciclopentil4-[2-(2-etil-5-metoxipiridin-4-il)etil]dihidro-2H-piran-2,4(3H)diona

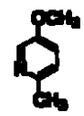


Se disolvió 6-[2-ciclopentil-4-(2-etil-5-metoxi-piridin-4-il)-2-hidraxy-but-3-inil]-2,2-dimetil[1,3]dioxin-4-ona (1,8 g, 4 mmol, de la etapa 8 mostrada a continuación) en EtOH (15 ml) y se trató con $Pd(OH)_2$ (0,5 g, 20% en peso, tipo Degussa). La mezcla se agitó en un globo de hidrógeno durante 2 horas. La mezcla de reacción se filtró a través de una capa de celite lavando con EtOAc. El filtrado se concentró hasta dar un sólido amarillo pálido.

El sólido se disolvió en metanol (10 ml), se trató con carbonato potásico (1,28g, 9,3 mmol) y se calentó a 45°C en una atmósfera de N_2 durante 60 minutos. La mezcla de reacción se repartió entre H_2O e IPE. La capa acuosa se neutralizó con HCl 1 N y se extrajo con EtOAc. Las capas orgánicas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron para dar el producto en forma de un sólido amarillo (0,71 g,51% de rendimiento). ^1H RMN (400 MHz, $CDCl_3$): δ 1,26 (t, J = 7,6 Hz, 3 H), 1,41-1,95 (m a, 8 H), 2,34 (m, 1H), 2,63-2,76 (m, 6 H), 3,43 (m, 2 H), 3,88 (m,5 H), 6,90 (s, 1H), 8,09 (s, 1H). Análisis calculado para $C_{20}H_{27}NO_4$: C, 69,54; H, 7,88; N, 4,05, Encon-

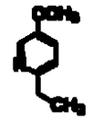
trado: C, 69,33; H, 7,88; N, 3,99.

Etapa 1: 5-Metoxi-2-metil-piridina



Se añadió 5-hidroxi-2-metilpiridina (15 g, 0,14 mol) a una suspensión agitada de KOH (31g, 0,55 mol) en DMSO (150 ml). La mezcla se agitó durante 1 hora y después se trató con yoduro de metilo (9,8 ml, 0,15 mol). Después de 20 minutos la mezcla de reacción se vertió en H_2O y se extrajo con éter. Los extractos de éter se secaron sobre $MgSO_4$ y se concentraron hasta dar un aceite rojo. La purificación por cromatografía en columna ultrarrápida (0% to 50% EtOAc en hexanos) dio el producto en forma de un aceite transparente (10,1g,59%). ^1H RMN (400 MHz, $CDCl_3$): δ 2,49 (s, 3 H), 3,83 (s, 3 H), 7,06 (d, J = 8,6 Hz, 1H), 7,12 (d, J = 8,3 Hz, 1H), 8,19 (d, J = 2,8 Hz, 1H).

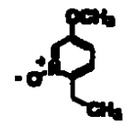
Etapa 2: 2-etil-5-metoxi-piridina



Se añadió 5-metoxi-2-metil-piridina (9,5 g, 77 mmol) a una solución enfriada a -78°C de LDA preparada a partir de n-BuLi (37 ml, 93 mmol, 2,5 M en hexanos) y diisopropilamina (13 ml, 93 mmol) disueltos en THF (100 ml). La mezcla de reacción de color rojo oscuro se agitó durante 30 minutos y después se trató con yoduro de metilo (5,4 ml, 85 mmol). Después de 2 horas la mezcla se inactivó con NH_4OH concentrado (15 ml). La mezcla se vertió en H_2O y se extrajo con EtOAc. Los extractos orgánicos se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron hasta dar un aceite rojo. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-40% en hexanos) dio el producto en forma de un aceite transparente (2,5 g, 24%) y material de partida sin reaccionar (3,8g, 40%). ^1H RMN (400 MHz, $CDCl_3$): δ 1,28 (t, J-7,3 Hz, 3 H), 2,76 (q, J = 7,3 Hz, 2 H), 3,84 (s, 3 H), 7,08 (d, J = 8,3 Hz, 1H), 7,14 (d, J = 8,3 Hz, 1H), 8,23 (s, 1H).

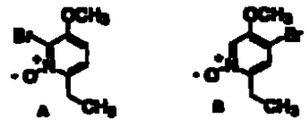
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Etapa 3: 1-óxido de 2-etil-5-metoxi-piridina



Se añadió ácido 3-cloroperoxibenzoico (5,66 g, 32,8 mmol) a una solución agitada de 2-etil-5-metoxi-piridina (3 g, 22 mmol) disuelta en $CHCl_3$ (100 ml). La reacción se agitó a temperatura ambiente durante 3 horas y después se interrumpió con Na_2SO_3 saturado. La mezcla de reacción se repartió entre H_2O y CH_2Cl_2. La capa orgánica se lavó con NaOH 1 N, se secó sobre Na_2SO_4 y se concentró hasta dar un aceite (3,3g, 99%). ^1H RMN (400 MHz, $CDCl_3$): δ 1,29 (t, J = 7,5 Hz, 3 H), 2,89 (q, J = 7,5 Hz, 2 H), 3,82 (s, 3 H), 6,86 (d, J = 8,4 Hz, 1H), 7,11 (d, J = 8,3 Hz, 1H), 8,04 (s, 1H).

Etapa 4: 1-Óxido de 2-bromo-6-etil-3-metoxi-piridina (A) y 1-óxido de 4-bromo-2-etil-5-metoxipiridina (B)

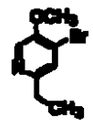


Se añadió lentamente ácido nítrico (6 ml) a una solución enfriada a 0°C de 1-óxido de 2-etil-5-metoxi-piridina (3,4 g, 22,2 mmol) disuelta en ácido sulfúrico (8 ml). La mezcla se calentó a 90°C durante 5 horas. La mezcla se vertió en hielo, se basificó con NaOH al 15% y se extrajo con EtOAc. Los extractos orgánicos se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron hasta dar un sólido amarillo. La purificación por cromatografía en columna ultrarrápida (0% a 50%) dio una mezcla de isómeros nitro en forma de un sólido amarillo (1,58g, 36%)

El sólido se disolvió en ácido acético (30 ml) y se trató con bromuro de acetilo (18 ml). La mezcla se calentó a 80°C durante 5 horas. La mezcla se vertió en hielo, se basificó con gránulos de NaOH y se extrajo con EtOAc. Las capas orgánicas se secaron sobre Na_2SO_4 y se concentraron hasta dar un sólido amarillo. La cromatografía en columna ultrarrápida (EtOAc al 0%-80% en hexanos) dio 1-óxido de 2-bromo-6-etil-3metoxi-piridina (0,329, 18%). La elución adicional con MeOH al 5% en CH_2Cl_2 dio 1-óxido de 4-bromo-2etil-5-metoxi-piridina (1,318, 74%). A: ^1H RMN (400 MHz, CDCl3): δ 1,30 (t, J =

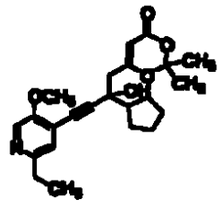
7,3 Hz, 3 H), 2,95 (q, J = 7,3 Hz, 2 H), 3,94 (s, 3 H), 6,79 (d, J = 8,8 Hz, 1H), 7,11 (d, J = 8,8 Hz, 1H). B: ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,29 (t, J = 7,3 Hz, 3 H), 2,86 (q, J-7,3 Hz, 2 H), 3,90 (s, 3 H), 7,36 (s, 1H), 7,98 (s, 1H).

Etapa 5: 4-Bromo-2-etil-5-metoxi-piridina



Se añadió tribromuro de fósforo (5,5 ml) a una solución de 1-óxido de 4-bromo-2-etil-5-metoxipiridina (1,25 g,5,4 mmol) disuelto en CH_2Cl_2 (40 ml). La mezcla de reacción se calentó a 50°C durante 1 hora. Después de enfriar a temperatura ambiente la mezcla se vertió en hielo y se basificó con NaOH al 15% y se extrajo con CH_2Cl_2. Los extractos orgánicos se secaron sobre Na_2SO_4 y se concentraron hasta un aceite transparente (1,13 g, 97%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,28 (t, J = 7,6 Hz, 3 H), 2,75 (q, J = 7,6 Hz, 2 H), 3,97 (s, 3 H), 7,37 (s, 1H), 8,13 (s, 1H).

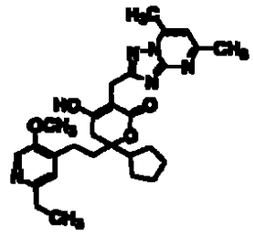
Etapa 6: 6-[2-ciclopentil-4-(2-etil-5-metoxi-piridin-4-il)-2-hidroxi-but-3-inil]-2,2-dimetil[1,3]dioxin-4-ona



Una mezcla de 4-bromo-2-etil-5-metoxi-piridina (1,1g,5,1 mmol), 6-(2-ciclopentil-2-hidroxibut-3-inil)-2,2-dimetil-4H-1,3-dioxin-4-ona (1,22 g, 4,6 mmol), $PdCl_2(PPh_3)_2$ (0,13 g, 4% en moles) y CuI (27 mg, 3% en moles) en diisopropilamina (6 ml) y DMF (6 ml) se calentó a 90°C durante 30 min. La mezcla de reacción se enfrió a temperatura ambiente y se repartió entre $NaHCO_3$ saturado y EtOAc. La capa orgánica se lavó con H_2O y salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un aceite de color pardo. La cromatografía en columna ultrarrápida (EtOAc al 0%-80% en hexanos) dio el producto en forma de un aceite amarillo (1,62, 89%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,26 (t, J = 7,6 Hz, 3 H), 1,60-1,84 (m a, 14 H), 2,26 (m, 1H), 2,71 (m,5 H), 3,91 (s, 3 H),5,54

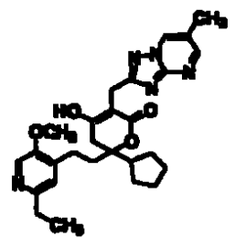
(s, 1H), 7,05 (s, 1H), 8,19 (s, 1H).

Ejemplo A(3): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2etil-5-metoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 6-ciclopentil-6-[2-(2-etil-5-metoxipiridin-4-il)etil]dihidro-2H-piran-2,4(3H)-diona (ejemplo A(2)) en lugar de 6-ciclopentil-6-[2-(5-etil-4hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona. ^{1}H RMN (400MHz, DMSO-d_6): δ 0,94 (t, J = 7,58 Hz, 3H), 1,19-1,53 (m, 8H), 1,83 (m, 1H), 1,91 (m, 1H), 2,20 (m, 4 H), 2,29-2,37 (m, 6H), 2,43 (q, J = 7,58 Hz, 2H), 2,59 (d, J = 17,2 Hz, 1H), 3,50 (d, J = 16,2 Hz, 1H), 3,56 (s, 3 H), 3,61 (d, J = 16,2 Hz, 1H), 6,83 (s, 1H), 6,85 (s, 1H), 7,88 (s, 1H), 10,82 (s, 1H). Análisis calculado para $C_{28}H_{35}N_5O_4$•0,5 AcOH: C, 65,03; H, 6,96; N, 13,08. Encontrado: C, 65,15; H, 7,05; N, 12,79.

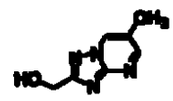
Ejemplo A(4): 6-ciclopentil-6-[2-(2-etil-5-metoxipiridin-4-il)etil]-4-hidroxi-3-[(6metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona



Se añadió 6-metil-[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído (0,13 g, 0,82 mmol, de la etapa 2 mostrada a continuación) a una solución de 6-ciclopentil-6-[2-(2-etil-5-metoxipiridin-4-il)etil]dihidro-2H-piran-2,4(3H)-diona (0,23g, 0,68 mmol, ejemplo A(2)) en MeOH (7 ml). La mezcla de reacción se agitó durante 10 minutos y después se trató con complejo de borano-diemtilamina (60 mg, 0,68 mmol). Después de 15 horas la

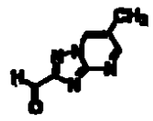
mezcla de reacción se filtró a través de una frita de vidrio lavando con MeOH. El filtrado se concentró para dar un aceite amarillo. La purificación por HPLC preparativa dio el producto en forma de un polvo blanco (58 mg, 17%). ^{1}H RMN (400 MHz, DMSO-d_6): δ 1,22 (t, J = 7,6 Hz, 3H), 1,42-1,75 (m, 8H), 2,11 (m, 2 H), 2,41 (s, 3 H), 2,46-2,65 (m, 4 H), 2,70 (q, J = 7,6 Hz, 2H), 2,83 (d, J = 17,7 Hz, 1H). 3,85 (m,5 H), 7,13 (s, 1H), 8,16(s, 1H) 8,74 (s, 1H), 8,93 (s, 1H), 11,04 (s, 1H). MS (ESI): 492,10 $(M+H)^+$.

Etapa 1: (6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metanol



A una suspensión de (5-amino-1H-[1,2,4]triazol-3-il)-metanol (16,6 g, 87,6 mmol) de la etapa 6 del ejemplo A(1) en ácido acético se le añadió 3-etoximetacroleína (10 g, 87,6 mmol). La mezcla se calentó a 80°C durante 4 horas. Después de la refrigeración de la solución, el producto se retiró de la solución por cristalización. El producto recogido fue un sólido blanco (14 g, 92%). ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,38 (s, 3 H), 4,63 (s, 2 H),5,52 (s, 1H), 8,75 (s, 1H), 9,21 (s, 1H).

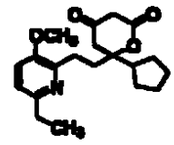
Etapa 2: 6-metil[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído



Una suspensión de (6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metanol (15,7 g, 95,6 mmol) de la etapa 1 anterior, TEMPO (112mg, 7,2 mmol), diacetato de yodobenceno (33,9 g, 105,2 mmol) en CH_2Cl_2 (100 ml) se agitó a temperatura ambiente durante 2 horas. Una vez que se consideró que la reacción se había completado, se añadió lentamente metil terc-butil éter (50 ml) para precipitar el producto. Las aguas madre concentradas se introdujeron en una columna de gel de sílice y se eluyeron con MeOH al 2%/CH_2Cl_2 para dar una cantidad adicional del producto aldehído en forma de un sólido blanco (12 g, 80%). ^{1}H RMN ($CDCl_3$) δ: 2,54 (s, 3 H), 8,73 (s, 1H), 8,85 (s, 1H), 10,23 (s, 1H).

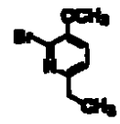
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Ejemplo A(5): 6-ciclopentil-6-[2-(6-etil-3-metoxipiridin-2-il)etil]dihidro-2H-piran-2,4(3H)diona



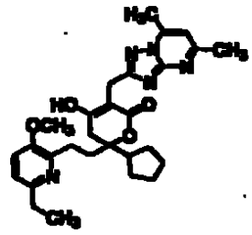
El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo 2-bromo-6-etil-3-metoxi-piridina de la etapa 1 mostrada a continuación en lugar de 4-bromo-2-etil-5-metoxi-piridina en la etapa 6 de ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,24 (t, J = 7,6 Hz, 3 H), 1,41-1,84 (m a, 8 H), 2,12 (m, 2 H), 2,37 (m, 1H), 2,72 (m, 4 H), 2,89 (m, 2 H), 3,42 (m, 2 H), 3,79 (s, 3 H), 6,96 (d, J = 8,3 Hz, 1H), 7,03 (d, J = 8,3 Hz, 1H). MS (ESI): 346,10 $(M+H)^+$

Etapa 1: 2-Bromo-6-etil-3-metoxi-piridina



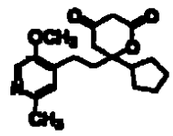
Se añadió tribromuro de fósforo (1,3 ml) a una solución de 1-óxido de 2-bromo-6-etil-3-metoxipiridina (0,3 g, 1,3 mmol, de la etapa 4 del ejemplo A(2)) disuelta en CH_2Cl_2 (10 ml). La mezcla de reacción se calentó a 50°C durante 1 hora. Después de enfriar a temperatura ambiente la mezcla se vertió en hielo y se basificó con NaOH al 15% y se extrajo con CH_2Cl_2. Los extractos orgánicos se secaron sobre Na_2SO_4 y se concentraron hasta dar un aceite transparente (0,28 g, 99%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,27 (t, J = 7,6 Hz, 3 H), 2,76 (d, J = 7,6 Hz, 2 H), 3,89 (s, 3 H), 7,06 (d, J = 8,1Hz, 1H), 7,09 (d, J = 8,1Hz, 1H).

Ejemplo A(6): 6-ciclopentil-3-(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2 il)metil]-6-[2-(6-etil-3-metoxipiridin-2-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



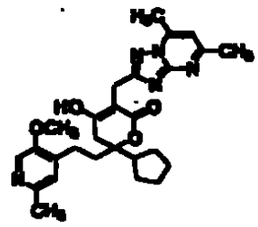
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 6-ciclopentil-6-[2-(6etil-3-metoxipiridin-2-il)etil]dihidro-2H-piran-2,4(3H)-diona (ejemplo A(5)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona. ^{1}H RMN (400 MHz, DMSO-d_6): δ 1,15 (t, J = 7,58 Hz, 3H), 1,42-1,75 (m, 8H), 2,11 (s, 1H), 2,22 (s, 1H), 2,34-2,65 (m, 11H), 2,74 (m, 2 H), 3,71 (s, 3 H), 3,73 (d, J = 16,4 Hz, 1H), 3,79 (d, J = 16,4 Hz, 1H), 7,02 (s, 1H), 7,04 (d, J = 8,6 Hz, 1H), 8,59 (d, J = 8,6 Hz, 1H), 10,91 (s, 1H). MS (ESI): 506,10 $(M+H)^+$.

Ejemplo A(7): 6-ciclopentil-6-[2-(5-metoxi-2-metilpiridin-4-il)etil]dihidro-2H-piran-2,4(3H)-diona



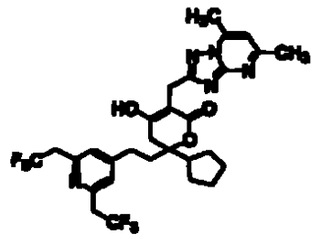
El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo 5-metoxi-2-metilpiridina de la etapa 1 del ejemplo A(2) en lugar de 2-etil-5-metoxi-piridina en la etapa 3 de ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,41-1,84 (m a, 8 H), 2,31 (m, 1H), 2,46 (s, 3 H), 2,67-2,76 (m, 4 H), 3,42 (s, 2 H), 3,88 (m,5 H), 6,91 (s, 1H), 8,04 (s, 1H). Análisis calculado para $C_{18}H_{25}NO_4$: C, 68,86; H, 7,60; N, 4,23, Encontrado: C, 68,92; H, 7,75; N, 4,26.

Ejemplo A(8): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-[2-(5-metoxi-2-metilpiridin-4-il)etil]-5,6-dihidro-2H-piran-2-ona



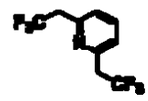
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 6-ciclopentil-6-[2-(5-metoxi-2-metilpiridin-4-il)etil]dihidro-2H-piran-2,4(3H)-diona (ejemplo A(7)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidropiran-2,4-diona. ^{1}H RMN (400 MHz, DMSO-d6): δ 1,45-1,78 (m, 8H), 2,11 (s, 1H), 2,19 (s, 1H), 2,41 (s, 3 H), 2,48 (m, 4 H), 2,56-2,62 (m, 6 H), 2,84 (d, J = 17,4 Hz, 1H), 3,76 (d, J = 16,0 Hz, 1H), 3,82 (s, 3 H), 3,88 (d, J = 16,0 Hz, 1H), 7,10 (s, 1H), 7,12 (s, 1H), 8,11 (s, 1H), 11,15 (s, 1H). Análisis calculado para $C_{27}H_{33}N_5O_4$•0,5 ACOH: C, 64,47; H, 6,76; N, 13,43, Encontrado: C, 64,42; H, 6,78; N, 13,39.

Ejemplo A(9): 6-{2-[2,6-Bis(2,2,2-trifluoroetil)piridin-4-il]etil}-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



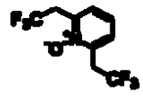
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 4-bromo-2,6-bis-(2,2,2-trifluoro-etil)-piridina de la etapa 5 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d6): δ 1,19-1,53 (m, 8H), 1,98 (m, 2H), 2,14-2,37 (m, 8H), 2,52 (m, 2H), 2,59 (d, J = 17,4 Hz, 1H), 3,50-3,67(m, 6 H), 6,86 (s, 1H), 7,20 (s, 2 H), 10,79 (s, 1H). MS (ESI): 612,15 $(M+H)^+$.

Etapa 1: 2,6-Bis-(2,2,2-trifluoro-etil)-piridina



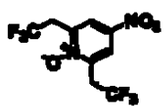
Se añadió trimetil(trifluorometil)silano (11,8 ml, 75,5 mmol) a una mezcla agitada de 2,6-bis(bromometil)piridina (8g, 30,2 mmol), KF (4,4 g, 75,5 mmol), CuI (17,3g, 90,6 mmol) en DMF (40 ml) y NMP (40 ml). La mezcla de reacción se calentó a 55°C en una atmósfera de N2 durante 15 horas. La mezcla se vertió en agua, se basificó con NaOH 1 N y se extrajo con EtOAc. Las capas orgánicas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron hasta dar un aceite negro. La cromatografía en columna ultrarrápida (EtOAc al 0%-30% en hexanos) dio el producto en forma de un aceite amarillo (4,3g,54%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 3,61 (q, J = 10,6 Hz, 4 H), 7,32 (d, J = 7,6 Hz, 2 H), 7,71 (d, J = 7,6 Hz, 1H).

Etapa 2: 1-Óxido de 2,6-bis-(2,2,2-trifluoro-etil)-piridina



Se añadió ácido 3-cloroperoxibenzoico (4,52 g, 26,2 mmol) a una solución de 2,6-bis-(2,2,2-trifluoroetil)-piridina (4,25 g, 17,5 mmol) en $CHCl_3$ (70 ml). La reacción se agitó a temperatura ambiente durante 4 horas y después se interrumpió con Na2SO3 saturado. Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2. Las capas orgánicas se lavaron con NaOH 1 N y salmuera, se secaron sobre Na_2SO_4 y se concentraron hasta dar un aceite amarillo. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-50% en hexanos) dio el producto en forma de un sólido amarillo (2,65 g,58%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 3,96 (q, J = 10,4 Hz, 4 H), 7,27 (t, J = 8,1Hz, 1H), 7,47 (d, J = 8,1Hz, 2H).

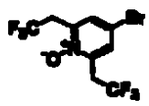
Etapa 3: 1-Óxido de 4-nitro-2,6-bis-(2,2,2-trifluoro-etil)-piridina



Se disolvió 1-óxido de 2,6-bis-(2,2,2-trifluoro-etil)-piridina (2,65 g, 10,22 mmol)

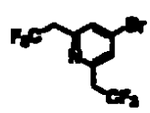
en H_2SO_4 (4 ml) y se enfrió a 0°C. Se añadió lentamente HNO_3 (3,2 ml) y después de completarse la adición, la mezcla de reacción se calentó a 90°C durante 2 horas. La mezcla se vertió en hielo, se basificó con NaOH al 15% y se extrajo con CH_2Cl_2. Las capas orgánicas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron hasta dar un aceite rojo (2,72 g, 81%). ^1H RMN (400 MHz, $CDCl_3$): δ 3,95 (t, J = 10,1Hz, 4 H), 8,31 (s, 2 H).

Etapa 4: 1-Óxido de 4-bromo-2,6-bis-(2,2,2-trifluoro-etil)-piridina



Se añadió bromuro de acetilo (14 ml) a una solución de 1-óxido de 4-nitro-2,6-bis-(2,2,2-trifluoro-etil)-piridina (2,7 g, 8,9 mmol) disuelto en AcOH (25 ml). La mezcla de reacción se calentó a 90°C durante 5 horas. La reacción se enfrió a temperatura ambiente, se vertió en hielo, se basificó con gránulos de NaOH y se extrajo con EtOAc. Las capas orgánicas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron hasta dar un aceite rojo. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-30% en hexanos) dio el producto en forma de un aceite amarillo (2,18 g, 72%). ^1H RMN (400 MHz, $CDCl_3$): δ 3,92 (t, J = 10,1Hz, 4 H), 7,59 (s, 2 H).

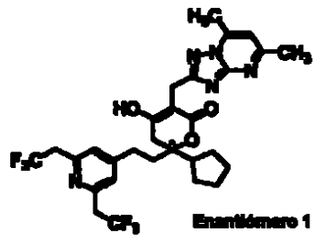
Etapa 5: 4-Bromo-2,6-bis-(2,2,2 trifluoro-etil)-piridina



Una solución de 1-óxido de 4-bromo-2,6-bis-(2,2,2-trifluoro-etil)-piridina (2,1 g, 6,2 mmol) y PBr_3 (1 ml) en CH_2Cl_2 (15 ml) se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se vertió en hielo, se basificó con NaOH al 15% y se extrajo con EtOAc. Las capas orgánicas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron para dar un sólido amarillo pálido (1,77g, 89%). ^1H RMN (400 MHz, $CDCl_3$): δ 3,59 (t, J = 10,4 Hz, 4 H), 7,51 (s, 2 H).

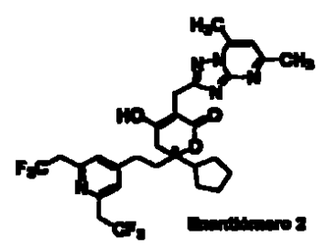
Ejemplo A(10): Enantiómero 1 de 6-(2-[2,6-Bis(2,2,2-trifluoroetil)piridin-4-il]etil)-6-

ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



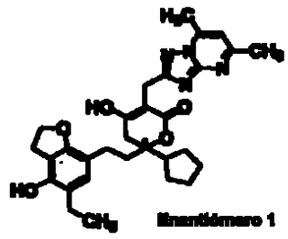
El compuesto del título se separó de la 6-{2-[2,6-Bis(2,2,2-trifluoroetil)piridin-4-il]etil}-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2ona racémica (65 mg, Ejemplo A(9)) usando HPLC quiral (Chiralpak AS-H, 100 bar, MeOH al 30%). (27 mg, tiempo de retención de 1,975 min, 100% ee)

Ejemplo A(11): Enantiómero 2 de 6-{2-[2,6-Bis(2,2,2-trifluoroetil)piridin-4-il]etil}-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se separó de la 6-{2-[2,6-bis(2,2,2-trifluoroetil)piridin-4-il]etil}-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (65 mg, Ejemplo A(9)) usando HPLC quiral (Chiralpak AS-H, 100 bar, MeOH al 30%). (29 mg, tiempo de retención 3,203 min, 100% ee)

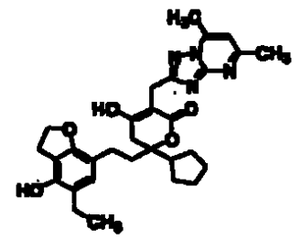
Ejemplo A(12): Enantiómero 1 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etil-4-hidroxi-2,3-dihidro-1-benzofuran-7-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



Enantómero 1

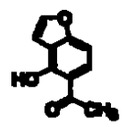
El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]6-[2-(5-etil-4-hidroxi-2,3-dihidro-1-benzofuran-7-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (280 mg, de la etapa 1 mostrada a continuación) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 40%). (113 mg, tiempo de retención de 5,140 min, 100% ee)

Etapa 1: 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etil-4-hidroxi-2,3-dihidro-1-benzofuran-7-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



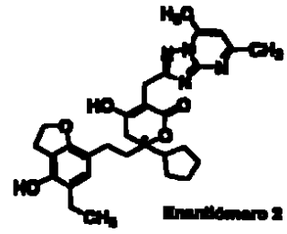
El compuesto del título se preparó de una forma análoga al ejemplo X(x) sustituyendo 1-(4-hidroxibenzofuran-5-il)-etanona de la etapa 1 mostrada a continuación en lugar de 1-(4-etoxi-2-hidroxifenil)-etanona en la etapa 2 de ese ejemplo.
^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,08 (t, J = 7,3 Hz, 3 H), 1,45-1,75 (m a, 8 H), 2,01 (m, 1H), 2,15 (m, 1H), 2,39-2,65 (m, 12 H), 2,80 (d, J = 17,4 Hz, 1H), 3,09 (t, J = 8,8 Hz, 2 H), 3,77 (d, J = 15,9 Hz, 1H), 3,85 (d, J = 15,9 Hz, 1H), 4,47 (t, J = 11,4 Hz, 2 H), 6,64 (s, 1H), 7,09 (s, 1H), 8,58 (s, 1H), 10,89 (s, 1H). Análisis calculado para $C_{30}H_{38}N_4O_5 \cdot 0,4H_2O$: C, 66,74; H, 6,87; N, 10,38, Encontrado: C, 66,71; H, 6,65; N, 10,21.

Etapa 1: 1-(4-Hidroxi-benzofuran-5-il)-etanona



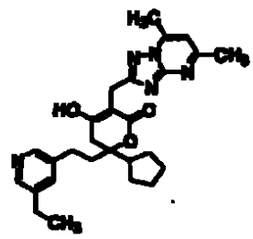
El compuesto del título se preparó como se describe en la siguiente referencia: *Tetrahedron* 1995,51, 4909-4922, ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,58 (s, 3 H), 7,00 (dd, J-2,0, 1,0 Hz, 1H), 7,05 (dd, J = 8,8, 1,0 Hz, 1H), 7,57 (d, J = 2,0 Hz, 1H), 7,66 (d, J = 8,8 Hz, 1H), 13,3 (s, 1H).

Ejemplo A(13): Enantiómero 2 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2il)metil]-6-[2-(5-etil-4-hidroxi-2,3-dihidro-1-benzofuran-7-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2-(5-etil-4-hidroxi-2,3-dihidro-1-benzofuran-7-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2 ona racémica (280 mg, de la etapa 1 del ejemplo A(12)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 40%). (106 mg, tiempo de retención de 8,992 min, 100% ee)

Ejemplo A(14): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etilpiridin-3-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(1) susti-

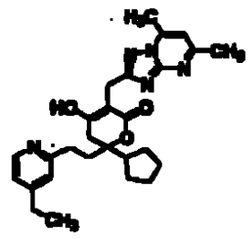
tuyendo 3-bromo-5-etilpiridina de la etapa 1 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ:1,14 (t, J = 7,6 Hz, 3 H), 1,40-1,70 (m a, 8 H), 2,14 (m, 2 H), 2,44-2,65 (m, 12 H), 2,79 (d, J = 17,6 Hz, 1H), 3,72 (d, J = 16,4 Hz, 1H), 3,83 (d, J = 16,4 Hz, 1H), 7,04 (s, 1H), 7,50 (s, 1H), 8,24 (s, 1H), 8,26 (s 1H), 10,90 (s, 1H). MS (ESI): 476,10 $(M+H)^+$

Etapa 1: 3-Bromo-5-etil-piridina



Una mezcla de NaOH (10 g, 0,25 mol), hidrazina monohidrato (10 ml) y 3-acetil-5bromopiridina (5 g, 25 mmol) suspendida en dietilenglicol (18 ml) se calentó a 140°C durante 6 horas. La mezcla se enfrió a temperatura ambiente y se repartió entre H_2O y éter. Los extractos de éter se secaron sobre $MgSO_4$ y se concentraron hasta dar un aceite transparente. La cromatografía en columna ultrarrápida (EtOAc al 0%-15% en hexanos) dio el producto en forma de un aceite transparente (2,9 g,58%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,26 (t, J = 7,6 Hz, 3 H), 2,65 (d, J = 7,6 Hz, 2 H), 7,67 (t, J = 2,0 Hz, 1H), 8,37 (d, J = 1,8 Hz, 1H), 8,51 (d, J = 2,0 Hz, 1H).

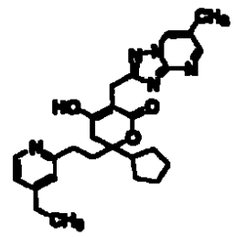
Ejemplo A(15): 6-ciclopentil-3-[(5,7,dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-{2-(4-etilpiridin-2-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 2-bromo-4-etilpiridina en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,99 (t, J = 7,6 Hz, 3 H), 1,22-1,53 (m a, 8 H), 2,06 (m, 2 H), 2,24-2,44 (m, 10 H), 2,59 (m, 3 H), 3,56 (d, J = 16,2 Hz, 1H), 3,65 (d, J = 16,2 Hz, 1H), 6,87 (s, 1H), 6,90 (d, J = 5,0 Hz, 1H), 6,97 (s, 1H),

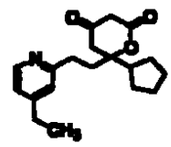
8,18 (d, J = 5,0 Hz, 1H), 10,77 (s, 1H). Análisis calculado para $C_{27}H_{33}N_5O_3 \cdot 0,25$ AcOH: C, 67,32; H, 6,99; N, 14,28, Encontrado: C, 67,31; H, 7,02; N, 13,92.

Ejemplo A(16): 6-ciclopentil-6-[2-(4-etilpiridin-2-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(4) sustituyendo 6-ciclopentil-6-[2-(4-etil-piridin-2-il)-etil]-dihidro-piran-2,4-diona (de la etapa 1 mostrada a continuación) en lugar de 6-ciclopentil.6-[2-(2-etil-5-metoxi-piridin-4-il)-etil]-dihidro-piran-2,4-diona. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,07 (t, J = 7,6 Hz, 3 H), 1,29-1,59 (m a, 8 H), 2,09 (m, 2 H), 2,26-2,52 (m, 6 H), 2,66 (m, 4 H), 3,64 (d, J = 16,2 Hz, 1H), 3,70 (d, J = 15,9 Hz, 1H), 6,97 (d, J = 5,0 Hz, 1H), 7,05 (s, 1H), 8,24 (d, J = 5,0 Hz, 1H), 8,59 (s, 1H), 8,86 (s, 1H), 10,82 (s, 1H). Análisis calculado para $C_{28}H_{31}N_5O_3 \cdot 0,3$ AcOH: C, 66,62; H, 6,77; N, 14,60, Encontrado: C, 66,63; H, 6,86; N, 14,24.

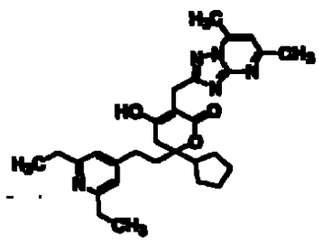
Etapa 1: 6-ciclopentil-6-[2-(4-etil-piridin-2-il)-etil]-dihidro-piran-2,4-diona



El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo 2-bromo-4-etilpiridina en lugar de 4-bromo-2-etil-5-metoxi-piridina en la etapa 6 de ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,25 (t, J = 7,6 Hz, 3 H), 1,41-1,82 (m a, 8 H), 2,14 (m, 2 H), 2,30 (m, 1H), 2,63 (q, J = 7,6 Hz, 2 H), 2,75 (m, 2 H), 2,86 (m, 2 H), 3,47 (m, 2 H), 7,01 (m, 2 H), 8,37 (s, 1H). MS (ESI): 316,10 $(M+H)^+$.

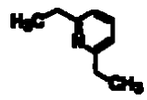
Ejemplo A(17): 6-ciclopentil-6-(2-(2,6-dietilpiridin-4-il)etil]-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-

ona



El compuesto del título se preparó de una forma análoga al ejemplo A(9) sustituyendo 2,6-dietil-piridina de la etapa 1 mostrada a continuación en lugar de 2,6-bis-(2,2,2-trifluoro-etil)-piridina en la etapa 2 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,16 (t, J = 7,6 Hz, 6 H), 1,40-1,72 (m a, 8 H), 2,13 (m, 2 H), 2,41-2,67 (m, 14 H), 2,78 (d, J = 17,1Hz, 1H), 3,70 (d, J = 16,4 Hz, 1H), 3,83 (d, J-16,4 Hz, 1H),6,91 (s, 2 H), 7,05 (s, 1H), 10,93 (s, 1H). Análisis calculado para $C_{28}H_{37}N_5O_3$•0,5 AcOH: C, 67,52; H, 7,37; N, 13,12, Encontrado: C, 67,70; H, 7,60; N, 12,91.

Etapa 1: 2,6-dietil-piridina



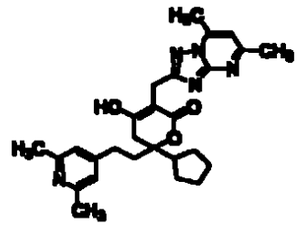
Una mezcla de NaOH (14,7 9, 0,37 mol), hidrazina monohidrato (15 ml) y 2,6-diacetilpiridina (6 g, 36,8 mmol) suspendida en dietilenglicol (27 ml) se calentó cuidadosamente a 120°C durante 16 horas. La mezcla se enfrió a temperatura ambiente y se repartió entre H_2O y éter. Los extractos de éter se lavaron con NaOH 1 N, se secaron sobre $MgSO_4$ y se concentraron hasta dar un aceite transparente. La cromatografía en columna ultrarrápida (EtOAc al 0%-15% en hexanos) dio el producto en forma de un aceite transparente (2,9 g,58%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,29 (t, J = 7,8 Hz, 3 H), 2,80 (d, J = 7,8 Hz, 2 H), 6,97 (d, J = 2,0 Hz, 2 H), 7,51 (t, J = 7,6 Hz, 1H).

Se preparó 2,6-dietil-piridina como se indica a continuación:

Una solución de bromuro de etilmagnesio en éter etílico [preparada a partir de Mg (16,5 g, 0,68 mol) y bromuro de etilo (50 ml, 0,68 mol) en 500 ml de éter] se añadió gota a gota a una mezcla de 2,6-dicloropiridina (50 g, 0,34 mol) y $NiCl_2$(dppp) (1,0 g, 2

mol) en éter etílico anhidro (500 M) a 0°C en una atmósfera de N_2. Después de la adición, la mezcla resultante se agitó a temperatura ambiente durante una noche, después se calentó a reflujo durante aproximadamente horas. La suspensión se vertió en hielo triturado (200 g) y la mezcla se saturó con NH_4Cl. La capa orgánica se separó y la fase acuosa se extrajo con éter (200 ml x 3). Las capas orgánicas combinadas se lavaron con agua y salmuera, se secaron sobre Na_2SO_4 y se concentraron para dar el producto (41,1g, 89%).

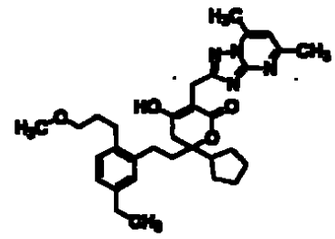
Ejemplo A(18): 6-ciclopentil-6-[2-(2,6-dimetilpiridin-4-il)etil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(9) sustituyendo N-óxido de 2,6-lutidina en lugar de 1-óxido de 2,6-bis-(2,2,2-trifluoro-etil)-piridina en la etapa 3 de ese ejemplo.

^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,44-1,75 (m a, 8 H), 2,19 (m, 2 H), 2,42-2,63 (m, 16 H), 2,85 (d, J = 17,7 Hz, 1H), 3,77 (d, J = 16,1Hz, 1H), 3,89 (d, J = 16,9 Hz, 1H), 6,97 (s, 2 H), 7,12 (s, 1H), 11,05 (s, 1H). MS (ESI): 476,20 $(M+H)^+$.

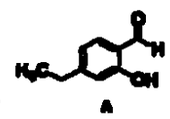
Ejemplo A(19): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2-[5etil-2-(3-metoxipropil)fenil]etil)-4-hidroxi-5,6-dihidro-2H-piran-2-ona



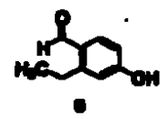
El compuesto del título se preparó de una forma análoga al ejemplo A(1) susti-

tuyendo 5-etil-2-(3-metoxi-propil)-fenil éster del ácido trifluorometanosulfónico de la etapa 5 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,08 (d, J = 7,6 Hz, 3 H), 1,40-1,73 (m a, 10 H), 1,99 (s, 1H), 2,18 (m, 1H), 2,33 (s, 3 H), 2,40-2,57 (m, 11H), 2,79 (d, J = 17,4 Hz, 1H), 3,16 (s, 3 H), 3,17 (d, J = 7,6 Hz, 2 H), 3,70 (d, J = 15,9 Hz, 1H), 3,81 (d, J = 15,9 Hz, 1H), 6,94 (m, 3 H), 7,01 (s, 1H), 10,95 (s, 1H). MS (ESI): 546,72 $(M+H)^+$.

Etapa 1: 4-etil-2-hidroxi-benzaldehído (A) y 2-etil-4-hidroxi-benzaldehído (B)



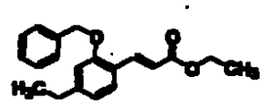
A



B

Se añadió cloruro de titanio (IV) (100 ml, 100 mmol, 1 M en $CH2Cl_2$) seguido de diclorometil metil éter (7,47 ml, 82,5 mmol) a una solución enfriada a 0°C de 3-etilfenol (6,118,50 mmol). La mezcla de reacción se agitó durante 45 minutos. La mezcla se vertió en hielo y se extrajo con EtOAc. Las capas orgánicas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron hasta dar un aceite rosa brillante. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-10% en hexanos) dio 4-etil-2-hidroxi-benzaldehído (4,9 g, 65%) seguido de 2-etil-4-hidroxi-benzaldehído (1,32 g, 18%). A: ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,25 (t, J = 7,6 Hz, 3 H), 2,67 (d, J-7,6 Hz, 2 H), 6,82 (s, 1H), 6,85 (d, J = 8,0 Hz, 1H), 7,46 (t, J = 8,0 Hz, 1H), 9,83 (s, 1H), 11,05 (s, 1H). B: ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,27 (t, J = 7,6 Hz, 3 H), 3,03 (d, J = 7,6 Hz, 2 H), 6,68 (s, 1H), 6,78 (s, 1H), 6,82 (d, J = 8,3 Hz, 1H), 7,77 (t, J = 8,3 Hz, 1H), 10,10 (s, 1H).

Etapa 2: éster etílico del ácido 3-(2-benciloxi-4-etil-fenil)-acrílico

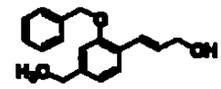


Se añadió carbonato potásico (8,84 g, 64 mmol) seguido de bromuro de bencilo (3,8 ml, 32 mmol) a una solución de 4-etil-2-hidroxi-benzaldehído (4,8 g, 32 mmol) en DMF (50 ml). La mezcla se agitó durante 15 horas y después se repartió entre HCl 1 N

y EtOAc. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un aceite de color pardo. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-10% en hexanos) dio el producto en forma de un aceite amarillo (6,1g, 84%).

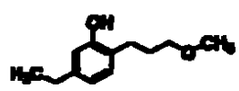
El aceite se disolvió en THF (40 ml) y se trató con (carbetoximetileno)trifenilfosforano (3,5 g, 9,99 mmol). La reacción se calentó a 70°C durante 5 días. La mezcla de reacción se concentró y se purificó por cromatografía en columna ultrarrápida (EtOAc al 0%-15% en hexanos) para dar el producto (2,93 g, 95%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,21 (t, J = 7,6 Hz, 3 H), 1,32 (t, J = 7,3 Hz, 3 H), 2,63 (d, J = 7,6 Hz, 2 H), 4,24 (q, J = 7,1Hz, 2 H),5,15 (s, 2 H), 6,49 (d, J = 16,2 Hz, 1H), 6,80 (m, 2 H), 7,33-7,47 (m, 6 H), 8,05 (d, J = 16,2 Hz, 1H).

Etapa 3: 3-(2-benciloxi-4-etil-fenil)-prop-2-en-1-ol



Se añadió una solución de éster etílico del ácido 3-(2-benciloxi-4-etil-fenil)-acrílico (2,9 g, 9,3 mmol) disuelto en éter (7 ml) a una suspensión enfriada a 0°C de hidruro de litio y aluminio (0,89 g, 23,4 mmol) en éter (20 ml). La mezcla de reacción se agitó durante 4 horas, se inactivó con H_2O (3,6 ml) y NaOH al 15% (0,9 ml) y después se filtró a través de una frita de vidrio lavando con éter. El filtrado se concentró hasta dar un aceite transparente y se purificó por cromatografía en columna ultrarrápida (EtOAc al 0%-30% en hexanos) para dar el producto (1,78 g,.71%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,22 (t, J = 7,6 Hz, 3 H), 2,62 (q, J = 7,6 Hz, 2 H), 4,29 (m, 2 H),5,10 (s, 2 H), 6,35 (dt, J = 16,2, 7,6 Hz, 1H), 6,78 (s, 1H), 6,80 (d, J = 7,1Hz, 1H), 6,95 (d, J = 16,2 Hz, 1H), 7,32-7,45 (m, 6 H).

Etapa 4: 5-etil-2-(3-metoxi-propil)-fenol

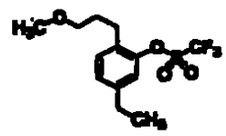


Se añadieron hidróxido potásico(1,17 g, 20,9 mmol) seguido de yoduro de metilo (0,5 ml, 7,8 mmol) a una solución de 3-(2-benciloxi-4-etil-fenil)-prop-2-en-1-ol (1,4

9,5,2 mmol) en DMSO (20 ml). La mezcla se agitó durante 15 horas y después se repartió entre HCl 1 N y EtOAc. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un aceite de color pardo. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-30% en hexanos) dio un aceite transparente (1,0 g, 68%).

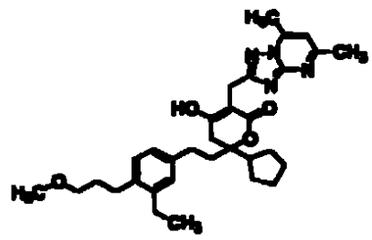
El aceite se disolvió en EtOH (10 ml) y se trató con $Pd(OH)_2$ (0,25 g, 20% en peso, tipo Degussa). La mezcla se agitó en un globo de hidrógeno durante 6 horas. La mezcla de reacción se filtró a través de una capa de celite lavando con EtOAc. El filtrado se concentró y se purificó por cromatografía en columna ultrarrápida para dar el producto (0,489, 85%). ^1H RMN (400 MHz, $CDCl_3$): δ 1,22 (t, J = 7,6 Hz, 3 H), 1,87 (m, 2 H), 2,58 (d, J = 7,6 Hz, 2 H), 2,69 (d, J = 6,6 Hz, 2 H), 3,37 (t, J = 5,8 Hz, 2 H), 3,41 (s, 3 H), 6,70 (d, J = 9,1Hz, 1H), 6,73 (s, 1H), 6,98 (m, 2 H).

Etapa 5: 5-etil-2-(3-metoxi-propil)-fenil éster del ácido trifluoro-metanosulfónico



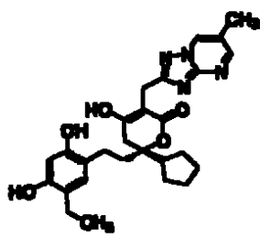
Se añadieron anhídrido trifluorometanosulfónico (0,47 ml, 2,8 mmol) seguido de trietilamina (0,42 ml, 3 mmol) a una solución enfriada a 0°C de 5-etil-2-(3-metoxi-propil)-fenol (0,45 g, 2,3 mmol). La reacción se agitó durante 1 hora y después se calentó a temperatura ambiente. La reacción se repartió entre HCl 1 N y EtOAc. Los extractos orgánicos se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron hasta dar un aceite negro. ^1H RMN (400 MHz, $CDCl_3$): δ 1,24 (t, J = 7,6 Hz, 3 H), 1,89 (m, 2 H), 2,65 (d, J = 7,6 Hz, 2 H), 2,75 (t, J = 7,6 Hz, 2 H), 3,35 (s, 3 H), 3,40 (t, J = 7,6 Hz, 2 H), 7,07 (s, 1H), 7,14 (d, J = 8,0 Hz, 1H), 7,23 (d, J = 8,0 Hz, 1H).

Ejemplo A(20): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2 il)metil]-4-(2-[3-etil-4-(3-metoxipropil)fenil]etil)-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(19) sustituyendo 2-etil-4-hidroxibenzaldehído de la etapa 1 del ejemplo A(19) en lugar de 4-etil-2-hidroxibenzaldehído en la etapa 2 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,97 (t, J-7,6 Hz, 3 H), 1,26-1,60 (m a, 10 H), 1,98 (m, 2 H), 2,31-2,45 (m, 14 H), 2,66 (d, J = 17,7 Hz, 1H), 3,14 (s, 3 H), 3,23 (t, J = 7,6 Hz, 2 H), 3,58 (d, J = 16,9 Hz, 1H), 3,71 (d, J = 16,9 Hz, 1H), 6,88 (m, 4 H), 10,98 (s, 1H). MS (ESI): 547,20 $(M+H)^+$.

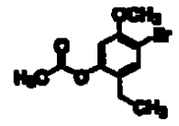
Ejemplo A(21): (6R)-ciclopentil-6-[2-(5-etil-2,4-dihidroxifenil)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona



Se añadió tribromuro de boro (0,82 ml, 1 M en CH_2Cl_2) a una solución enfriada a -78°C *de* 6-ciclopentil-6-[2(5-etil-4-hidroxi-2-metoxi-fenil)-etil]-4-hidroxi-3-(6-metil-[1,2,4]triazolo[1,5-a]pirimidin-2-*ilmetil*)-5,6-dihidro-piran-2-ona (70 mg, 0,14 mmol, de la etapa 3 mostrada a continuación) disuelta en CH_2Cl_2 (5 ml). La reacción se agitó durante 15 horas. Se añadió HCl 1 N y la reacción se agitó durante 10 minutos. La mezcla se extrajo con MeOH al 10% en EtOAc. Las capas orgánicas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron hasta dar un residuo sólido de color pardo. La purificación por HPLC preparativa dio el producto en forma de un sólido pardo (27 mg, 40%). ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,04 (t, J = 7,3 Hz, 3 H), 1,40-1,75 (m a, *8 H), 1,98 (m,* 2 H), 2,37-2,45 (m, 8 H), 2,57 (d, J = 17,4 Hz, 1H), 2,74 (d, J = 17,4 Hz, 1H), 3,78 (d, J = 16,1Hz, 1H), 3,79 (d, J = 16,1Hz, 1H), 6,33 (s, 1H), 6,68 (s, 1H), *8,69 (s,* 1H), 8,84 (m. 3 H), 10,90 (s, 1H). MS (ESI): 492,55 $(M+H)^+$.

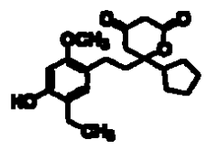
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474

Etapa 1: 4-bromo-2-etil-5-metoxi-fenil éster del ácido acético



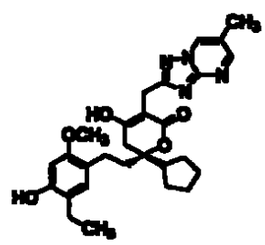
El compuesto del título se preparó de una forma análoga a la etapa 4 del ejemplo A(22) sustituyendo yoduro de metilo en lugar de yoduro de etilo en la etapa 1 de ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,16 (t, J = 7,4 Hz, 3 H), 2,32 (s, 3 H), 2,45 (q, J = 7,4 Hz, 2 H), 3,85 (s, 3 H), 6,59 (s, 1H), 7,42 (s, 1H).

Etapa 2: 6-ciclopentil-4-[2-(5-etil-4-hidroxi-2-metoxi-fenil)-etil]-dihidro-piran-2,4-diona



El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo 4-bromo-2etil-5-metoxi-fenil éster del ácido acético en lugar de 4-bromo-2-etil-5-metoxi-piridina en la etapa 6 de ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,20 (t, J = 7,4 Hz, 3 H), 1,41-1,86 (m, 9 H), 1,94 (m, 1H), 2,34 (m, 1H), 2,52 (m, 3 H), 2,62 (m, 1H), 2,73 (d, J = 16,4 Hz, 1H), 2,78 (d, J = 16,4 Hz, 1H), 3,41 (s, 2 H), 3,75 (s, 3 H), 4,58 (s, 1H), 6,35 (s, 1H), 6,80 (s, 1H).

Etapa 3: 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-metoxi-fenil)-etil]-4-hidroxi-3-(6-metil-[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil)-5,6-dihidro-piran-2-ona

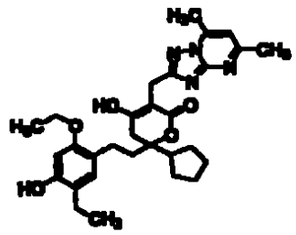


La 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-metoxi-fenil)-etil]-4-hidroxi-3-(6-metil-

[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil)-5,6-dihidro-piran-2-ona racémica se preparó de una forma análoga al ejemplo A(4) sustituyendo 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-metoxi-fenil)-etil]-dihidro-piran-2,4-diona de la etapa 2 anterior en lugar de 6-ciclopentil-6-[2-(2-etil-5-metoxipiridin-4-il)etil]dihidro-2H-piran-2,4(3H)-diona.

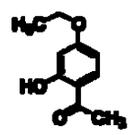
El compuesto del título se separó de la 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-metoxi-fenil)-etil]-4-hidroxi-3-(6-metil-[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil)-5,6-dihidro-piran-2-ona racémica usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 40%). (tiempo de retención 5,65 min). ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,10 (t, J = 7,6 Hz, 3 H), 1,44-1,76 (m a, 8 H), 2,04 (m, 2 H), 2,41-2,62 (m, 9 H), 2,81 (d, J = 17,4 Hz, 1H), 3,69 (s, 3 H), 3,79 (d, J = 16,2 Hz, 1H), 3,85 (d, J = 16,2 Hz, 1H), 6,44 (s, 1H), 6,82 (s, 1H), 8,74 (s, 1H), 8,88 (s, 1H), 9,10 (s, 1H), 10,95 (s, 1H).

Ejemplo A(22): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2 il)metil]-6-[2-(2-etoxi-5-etil-4-hidroxifenil)etil-4-hidroxi-5,6-dihidro-2H-piran-2-ona



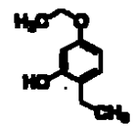
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo ácido acético 4-bromo-5-etoxi-2-etil-fenil éster de la etapa 4 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,80 (t, J-7,3 Hz, 3 H), 1,03 (t, J-6,8 Hz, 3 H), 1,24-1,52 (m a, 8 H), 1,70 (m, 1H), 1,85 (m, 1H), 2,12-2,32 (m, 11H), 2,37 (d, J = 17,4 Hz, 1H), 2,55 (d, J = 17,4 Hz, 1H), 3,51 (d, J = 16,2 Hz, 1H), 3,61 (m, 3 H), 6,13 (s, 1H), 6,51 (s, 1H), 6,83 (s, 1H), 8,76 (s, 1H), 10,61 (s, 1H). MS (ESI): 536,20 $(M+H)^+$

Etapa 1: 1-(4-etoxi-2-hidroxi-fenil)-etanona



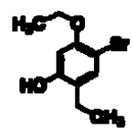
Se añadieron carbonato potásico (13,6 g, 99 mmol) seguido de yoduro de etilo (2,4 ml, 29,6 mmol) a una solución de 2',4'-dihidroxiacetofenona (5 g, 33 mmol) en DMF (50 ml). La mezcla se agitó durante 4 horas y después se repartió entre H_2O y EtOAc. La capa orgánica se lavó con NaHCO3 saturado y salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un aceite transparente. La purificación por cromatografía en columna dio el producto en forma de un sólido blanco (3,7g, 63%). ^1H RMN (400 MHz, $CDCl_3$): δ 1,43 (t, J = 6,8 Hz, 3 H), 2,55 (s, 3 H), 4,07 (d, J = 7,1Hz, 2 H), 6,40 (s, 1H), 6,43 (d, J-8,8 Hz, 1H), 7,62 (d, J = 8,8 Hz, 1H), 12,74 (s, 1H).

Etapa 2: 5-etoxi-2-etil-fenol



Se trató 1-(4-etoxi-2-hidroxi-fenil)-etanona disuelta en MeOH (40 ml) con Pd al 10%/C (1,4 g, tipo Degussa) y se agitó en un globo de H_2 durante 24 horas. La mezcla de reacción se filtró a través de una capa de celite lavando con EtOAc. El filtrado se concentró para dar el producto en forma de un aceite (3,12 g, 97%). ^1H RMN (400 MHz, $CDCl_3$): δ 1,21 (t, J = 7,6 Hz, 3 H), 1,39 (t, J = 7,1Hz, 3 H), 2,56 (d, J = 7,6 Hz, 2 H), 3,98 (d, J = 7,1Hz, 2 H), 4,79 (s, 1H), 6,37 (d, J = 2,5 Hz, 1H), 6,44 (dd, J = 8,3, 2,5 Hz, 1H), 7,01 (d, J = 8,3 Hz, 1H).

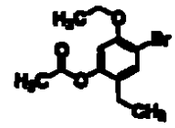
Etapa 3: 4-Bromo-5-etoxi-2-etil-fenol



Una solución de tribromuro de tetrabutil amonio (9,9 g, 20,5 mmol) en $CHCl_3$ (60 ml) se añadió a una solución agitada de 5-etoxi-2-etil-fenol (3,1 g, 18,6 mmol) disuelto en $CHCl_3$ (90 ml). La mezcla de reacción se agitó durante 30 minutos y después se inactivó con una solución al 5% de tiosulfato sódico (30 ml). La mezcla bifásica se agitó durante 30 minutos y después las capas se separaron. La capa orgánica se lavó con HCl 1 N y salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un aceite rojo. La

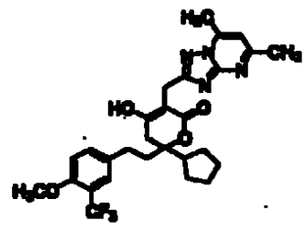
purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-15% en hexanos) dio el producto en forma de un aceite (2,6 g,58%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,20 (t, J = 7,6 Hz, 3 H), 1,44 (t, J = 7,1Hz, 3 H), 2,53 (q, J = 7,6 Hz, 2 H), 4,03 (q, J = 7,1Hz, 2 H), 4,85 (s, 1H), 6,41 (s,1H), 7,25 (s, 1H),

Etapa 4: 4-bromo-5-etoxi-2-etil-fenil éster del ácido acético



Se añadieron (0,91 ml, 12,8 mmol) seguido de trietilamina (1,8 ml, 12,8 mmol) a una solución agitada de 4-bromo-5-etoxi-2-etil-fenol (2,6 g, 10,7 mmol) disuelto en CH_2Cl_2 (20 ml). La reacción se agitó durante 45 minutos y después se repartió entre HCl 1 N y EtOAc. La capa orgánica se lavó con NaHCO3 saturado y salmuera, se secó sobre Na_2SO_4 y se concentró. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-20% en hexanos) dio el producto en forma de un aceite transparente (1,64 g,53%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,16 (t, J = 7,6 Hz, 3 H), 1,45 (t, J = 7,1Hz, 3 H), 2,31 (s, 3 H), 2,45 (q, J = 7,6 Hz, 2 H), 4,05 (q, J = 7,1Hz, 2 H), 6,58 (s, 1H), 7,41 (s, 1H).

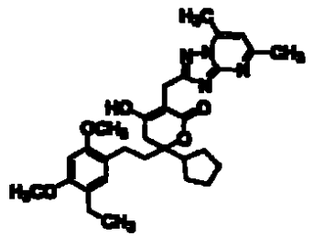
Ejemplo A(23): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-[2-[4-metoxi-3-(trifluorometil)fenil]etil]-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 4-bromo-2(trifluorometil)anisol en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxibenceno en la etapa 4 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,19-1,51 (m a, 8 H), 1,93 (m, 2 H), 2,212,46 (m, 10 H), 2,60 (d, J = 17,4 Hz, 1H), 3,53 (d, J = 16,2 Hz, 1H), 3,64 (d, J = 16,2 Hz, 1H), 3,67 (s, 3 H), 6,87 (s, 1H), 7,00 (d, J = 8,6 Hz, 1H),

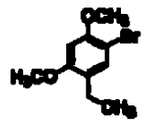
7,22 (d, J = 2,0 Hz, 1H), 7,40 (d, J = 17,4 Hz, 1H), 10,76 (s, 1H). MS (ESI): 545,10 $(M+H)^+$.

Ejemplo A(24): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etil-2,4-dimetoxifenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al Ejemplo A(1) sustituyendo 1-bromo-5-etil-2,4dimetoxi-benceno de la etapa 1 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,82 (d, J = 7,6 Hz, 3 H), 1,22-1,52 (m a, 8 H), 1,72 (m, 1H), 1,88 (m, 1H), 2,20-2,40 (m, 12 H), 2,56 (d, J = 17,9 Hz, 1H), 3,43 (s, 3 H), 3,52 (d, J = 18,1Hz, 1H), 3,58 (s, 3 H), 3,61 (d, J = 18,1Hz, 1H), 6,32 (s, 1H), 6,63 (s, 1H), 6,84 (s, 1H), 10,70 (s, 1H). MS (ESI): 535,20 $(M+H)^+$

Etapa 1: 1-Bromo-5-etil-2,4-dimetoxi-benceno

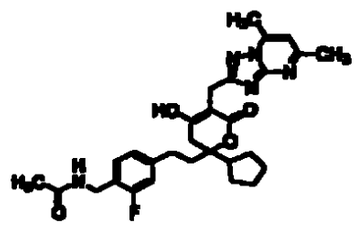


Una solución de tribromuro de tetrabutil amonio (15,4 g, 31,8 mmol) en $CHCl_3$ (100 ml) se añadió a una solución agitada de 4-etil resorcinol (4 g, 29 mmol) disuelto en $CHCl_3$ (50 ml). La mezcla de reacción se agitó durante 2 horas y después se inactivó con una solución al 5% de tiosulfato sódico (30 ml). La mezcla bifásica se agitó durante 30 minutos y después las capas se separaron. La capa orgánica se lavó con HCl 1 N y salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un aceite amarillo.

El aceite se disolvió en DMF (60 ml) y se trató con K_2CO_3 (12,7 g, 92 mmol), seguido de yoduro de metilo (2,9 ml, 46 mmol). La mezcla se agitó durante 15 horas y después se repartió entre H_2O y EtOAc. Las capas orgánicas se lavaron con HCl 1 N y

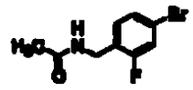
salmuera, se secaron sobre Na_2SO_4 y se concentraron hasta dar un aceite de color rojo oscuro. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-10% en hexanos) dio el producto en forma de un aceite amarillo (2,8 g, 39%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,15 (t, J = 7,6 Hz, 3 H), 2,54 (q, J = 7,6 Hz, 2 H), 3,83 (s, 3 H), 3,89 (s, 3 H), 6,46 (s, 1H), 7,26 (s, 1H).

Ejemplo A(25): N-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-fluorobencil]acetamida



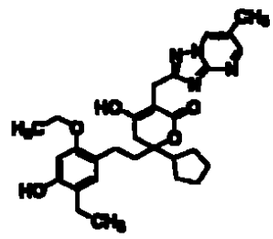
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 4-bromo-2-(trifluorometil)anisol en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxibenceno en la etapa 4 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,38-1,69 (m a, 8 H), 1,86 (s, 3 H), 2,12 (m, 2 H), 2,39-2,63 (m, 10 H), 2,77 (d, J = 17,2 Hz, 1H), 3,71 (d, J = 16,2 Hz, 1H), 3,83 (d, J = 16,2 Hz, 1H), 4,23 (d, J = 5,8 Hz, 2 H), 7,04 (m, 3 H), 7,21 (t, J = 7,8 Hz, 1H), 8,29 (t, J = 5,8 Hz, 1H), 10,99 (s, 1H). MS (ESI): 536,20 $(M+H)^+$

Etapa 1: N-(4-Bromo-2-fluoro-bencil)-acetamida



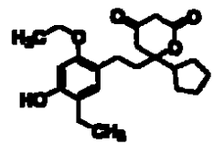
Se añadieron cloruro de acetilo (0,7 ml, 9,9 mmol) seguido de trietilamina (2,8 ml, 19,9 mmol) a una suspensión de hidrocloruro de 4-bromo-2-fluorobencilamina (29, 8,3 mmol) en CH_2Cl_2 (20 ml). La mezcla se agitó durante 90 minutos y después se repartió entre HCl 1 N y EtOAc. Las capas orgánicas se sometieron a salmuera, se secaron sobre Na_2SO_4 y se concentraron. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-60% en hexanos) dio el producto en forma de un aceite transparente (1,5 9, 74%). MS (ESI): 246,10, 248,10 $(M+H)^+$

Ejemplo A(26): 6-ciclopentil-6-[2-(2-etoxi-5-etil.4-hidroxifenil)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(4) sustituyendo 6-ciclopentil-6-(2-(2-etoxi-5-etil-4-hidroxi-fenil)-etil]-dihidro-piran-2,4-diona de la etapa 1 mostrada a continuación en lugar de 6-ciclopentil-6-[2-(2-etil-5-metoxi-piridin-4-il)-etil]-dihidro-piran-2,4-diona. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,08 (t, J = 7,3 Hz, 3 H), 1,32 (t, J = 6,8 Hz, 3 H), 1,46-1,77 (m a, 8 H), 2,03 (m, 2 H), 2,40 (s, 3 H), 2,44-2,56 (m, 6 H), 2,80 (d, J = 17,2 Hz, 1H), 3,78 (d, J = 15,7 Hz, 1H), 3,83 (d, J = 15,7 Hz, 1H), 3,91 (q, J = 7,1Hz, 2 H), 6,42 (s, 1H), 6,80 (s, 1H), 8,73 (s, 1H), 8,90 (s, 1H), 9,04 (s, 1H), 10,98 (s, 1H). Análisis calculado para $C_{29}H_{38}N_4O_6 \cdot 0,25\ H_2O$: C, 66,33; H, 7,01; N, 10,67, Encontrado: C, 66,57; H, 7,07; N, 10,28.

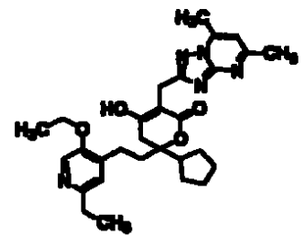
Etapa 1: 6-ciclopentil-6-[2-(2-etoxi-5-etil-4-hidroxi-fenil)-etil]-dihidro-piran-2,4-diona



El compuesto del título se preparó de una forma análoga a la etapa 5 del ejemplo A(1) sustituyendo 4bromo-5-etoxi-2-etil-fenil éster del ácido acético de la etapa 4 del ejemplo A(22) en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en la etapa 4 del ejemplo A(1). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,19 (t, J = 7,6 Hz, 3 H), 1,38 (t, J = 6,8 Hz, 3 H), 1,62-1,85 (m a, 9 H), 1,98 (m, 1H), 2,33 (m, 1H), 2,51 (m, 3 H), 2,62 (m, 1H), 2,73 (d, J = 16,2 Hz, 1H), 2,78 (d, J = 16,2 Hz, 1H), 3,42 (m, 2 H), 3,95 (q, J = 7,1Hz, 2 H), 4,98 (s a, 1H), 6,33 (s, 1H), 6,79 (s, 1H).

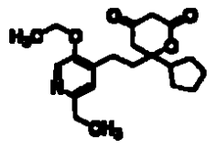
~~485~~
487

Ejemplo A(27): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



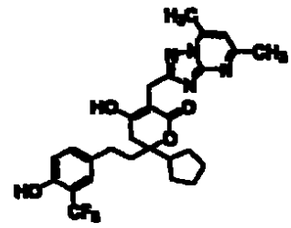
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 6-ciclopentil-6-[2-(5etoxi-2-etil-piridin-4-il)-etil]-dihidro-piran-2,4-diona de la etapa 1 mostrada a continuación en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,19 (t, J = 7,6 Hz, 3 H), 1,31 (t, J = 6,8 Hz, 3 H), 1,40-1,78 (m a, 8 H), 2,03-217 (m, 2 H), 2,48-2,72 (m, 12 H), 2,85 (d, J = 17,4 Hz, 1H), 3,76 (d, J = 16,4 Hz, 1H), 3,87 (d, J = 16,2 Hz, 1H), 4,08 (m, 2 H), 7,09 (m, 2 H), 8,13 (s, 1H), 10,96 (s, 1H). MS (ESI): 520,20 $(M+H)^+$

Etapa 1: 6-ciclopentil-6-[2-(5-etoxi-2-etil-piridin-4-il)-etil]-dihidro-piran-2,4-diona



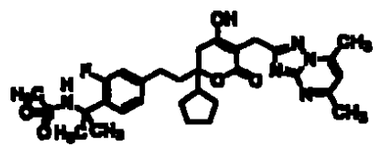
El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo yoduro de *etilo* en lugar de yoduro de *metilo* en la *etapa 1* de ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,26 (t, J = 7,6 Hz, 3 H), 1,43 (t, J = 6,8 Hz, 3 H), 1,50-2,05 (m a, 9 H), 2,34 (m, 2 H), 2,62-2,77 (m, 6 H), 3,44 (m, 2 H), 4,11 (q, J = 6,8 Hz, 2 H), 6,90 (s, 1H), 8,08 (s, 1H).

Ejemplo A(28): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-[2-[4-hidroxi-3-(trifluorometil)fenil]etil]-5,6-dihidro-2H-piran-2-ona



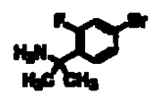
El compuesto del título se preparó de una forma análoga al ejemplo A(22) sustituyendo 2hidroxibenzotrifluoruro en lugar de 5-etoxi-2-etil-fenol en la etapa 3 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,39-1,71 (m a, 8 H), 2,09 (m, 2 H), 2,39-2,60 (m, 10 H), 2,77 (d, J = 17,7 Hz, 1H), 3,71 (d, J = 16,2 Hz, 1H), 3,83 (d, J = 16,2 Hz, 1H), 6,96 (d, J = 8,6 Hz, 1H), 7,06 (s, 1H), 7,29 (s, 1H), 7,38 (d, J = 9,8 Hz, 1H), 10,29 (s, 1H), 10,95 (s, 1H). Análisis calculado para $C_{27}H_{29}N_4O_4F_3$•1,0 AcOH: C,58,87; H,5,63; N, 9,49, Encontrado: C,59,13; H,5,89; N, 9,44.

Ejemplo A(29): N-(1-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-fluorofenil]-1-metiletil}metanosulfonamida



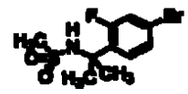
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo N-[1-(4-bromo-2-fluoro-fenil)-1-metil-etil]-metanosulfonamida de la etapa 2 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,31 - 1,41 (m, 1H) 1,54 (s, 3 H) 1,55 - 1,70 (m,5 H) 1,73 (s, 6 H) 1,98 (dd, J = 9,98, 7,16 Hz, 2 H) 2,29 - 2,39 (m, 1H) 2,55 - 2,69 (m, 9 H) 2,73 - 2,81 (m, 4 H) 4,05 (s, 2 H) 5,03 (s, 1H) 6,84 (t, J = 6,69 Hz, 2 H) 6,90 (d, J = 8,10 Hz, 1H) 7,25 (d, J = 16,77 Hz, 1H). MS (ESI): 600 $(M+H)^+$.

Etapa 1: 1-(4-Bromo-2-fluoro-fenil)-1-metil-etilamina



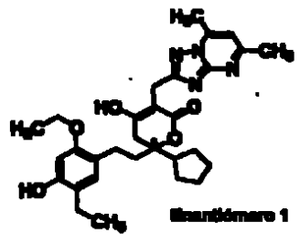
Se deshidrató $CeCl_3 \cdot 7H_2O$ (29,7g, 80 mmol) durante 2 horas al vacío a 150°C. Después de enfriar a 0°C, se añadió THF (anhidro, 640 ml) y la suspensión se agitó durante 2 h a temperatura ambiente. La suspensión se enfrió a -78°C y se añadió MeLi (1,6M en éter dietílico,50 ml). La mezcla se agitó durante 30 min, después se añadió 4-bromo-2-fluorobenzonitrilo (4 g, 20 mmol) y se agitó a esta temperatura durante 5 h. La temperatura se incrementó a 0°C, se añadió lentamente NH_4OH concentrado (50 ml) y la suspensión se filtró a través de Celite. La capa acuosa se acidificó con HCl 1 N (ac) y se lavó con acetato de etilo. La capa acuosa se basificó con NaOH (ac) 3 N y se extrajo con diclorometano. Se repitieron la síntesis y tratamiento y los lotes se combinaron, se secaron (Na_2SO_4), se filtraron y se concentraron al vacío para dar un aceite incoloro (1,25 g, 14%). ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,51 (s, 6 H) 1,66 (s, 2 H) 7,17 - 7,24 (m, 2 H) 7,30 - 7,37 (m, 1H).

Etapa 2: N-[1-(4-Bromo-2-fluoro-fenil)-1-metil-etil]-metanosulfonamida



A 1-(4-bromo-2-fuoro-fenil)-1-metil-etilamina (1,2 g,5,4 mmol) y trietilamina (900 µL, 6,5 mmol) en diclorometano (10 ml) a temperatura ambiente se les añadió cloruro de metanosulfonilo (500 µl, 6,5 mmol). La solución se agitó durante 16 h, se diluyó en HCl 1 N(ac) y se extrajo con acetato de etilo. La capa orgánica se lavó con bicarbonato sódico saturado y después con cloruro sódico saturado, se secó (Na_2SO_4), se filtró y se concentró *al vacío* hasta dar un sólido blanquecino. La cromatografía ultrarrápida (SiO_2, acetato de etilo al 40%/hexano) dio un sólido blanco (950 mg,57%). ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,76 (s, 6 H) 2,74 (s, 3 H) 4,88 (s, 1H) 7,24 (d, J = 1,51Hz, 1H) 7,27 - 7,30 (m, 2 H)

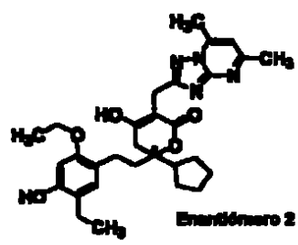
Ejemplo A(30): Enantiómero 1 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etoxi-5-etil-4-hidroxifenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



Enantiómero 1

El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etoxi-5-etil-4-hidroxifenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (120 mg, Ejemplo A(22)) usando HPLC quiral (Chiralpak AS-H, 115 bar, MeOH al 55%). (47 mg, tiempo de retención 1,89 min, 100% ee)

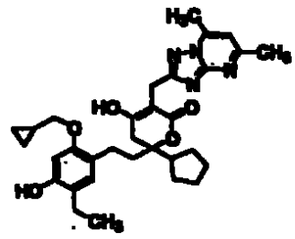
Ejemplo A(31): Enantiómero 2 de 6-ciclopentil-3-((5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etoxi-5-etil-4-hidroxifenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



Enantiómero 2

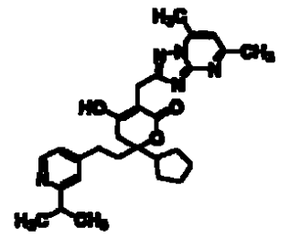
El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etoxi-5-etil-4-hidroxifenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (120 mg, Ejemplo A(22)) usando HPLC quiral (Chiralpak AS-H, 115 bar,55% MeOH). (43 mg, tiempo de retención 3,429 min, 99% ee)

Ejemplo A(32): 6-ciclopentil-4-[2-[2-(ciclopropilmetoxi)-5-etil-4-hidroxifenil]etil]-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(22) sustituyendo (bromometil)ciclopropano en lugar de yoduro de etilo en la etapa 1 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,02 (d, J = 4,8 Hz, 2 H), 0,28 (d, J = 8,6 Hz, 2 H), 0,75 (t, J = 7,6 Hz, 3 H), 0,80 (m, 1H), 1,18-1,51 (m a, 8 H), 1,72 (m, 1H), 1,82 (m, 1H), 2,09-2,52 (m, 13 H), 3,41 (d, J = 6,8 Hz, 2 H), 3,47 (d, J = 15,9 Hz, 1H), 3,55 (d, J = 15,9 Hz, 1H), 6,08 (s, 1H), 6,47 (s, 1H), 6,79 (s, 1H), 8,70 (s, 1H), 10,56 (s, 1H). MS (ESI): 561,25 $(M+H)^+$

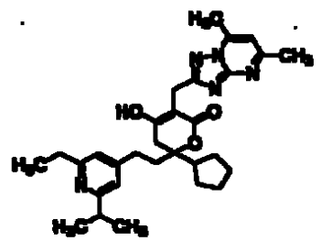
Ejemplo A(33): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2 il)metil]-4-hidroxi-6-[2-(2-isopropilpiridin-4-il)etil]-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(10) sustituyendo 2-isopropilpiridina en lugar de 2,6-bis-(2,2,2-trifluoro-etil)-piridina en la etapa 2 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,10 (d, J = 6,8 Hz, 6 H), 1,28-1,59 (m a, 8 H), 2,03 (m, 2 H), 2,31-2,54 (m. 10 H), 2,67 (d, J = 17,4 Hz, 1H), 2,67 (m, 1H), 3,60 (d, J = 16,2 Hz, 1H), 3,73 (d, J = 16,2 Hz, 1H), 6,85 (s, 1H), 7,01 (s, 2 H), 8,25 (d, J = 5,8 Hz, 1H), 10,85 (s, 1H).

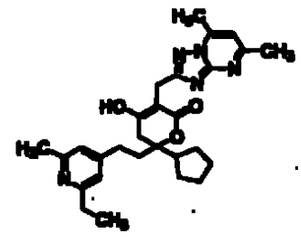
Análisis calculado para $C_{28}H_{35}N_5O_3 \cdot 0,7EtOAc$: C, 67,10; H, 7,42; N, 12,70, Encontrado: C, 67,24; H, 7,61; N, 12,68.

Ejemplo A(34): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2etil-6-isopropilpiridin-4il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



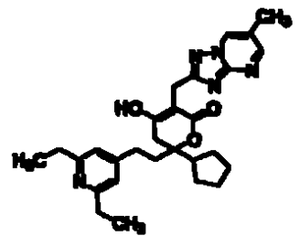
El compuesto del título se preparó de una forma análoga al ejemplo A(9) sustituyendo 2-etil-6isopropilpiridina en lugar de 2,6-bis-(2,2,2-trifluoro-etil)-piridina en la etapa 2 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,03 (m, 9 H), 1,24-1,55 (m a, 8 H), 2,00 (m, 2 H), 2,28-2,55 (m, 12 H), 2,63 (d, J = 17,4 Hz, 1H), 2,79 (m, 1H), 3,57 (d, J = 16,2 Hz, 1H), 3,69 (d, J = 16,2 Hz, 1H), 6,77 (s, 2 H), 6,91 (s, 1H), 10,79 (s, 1H). Análisis calculado para $C_{30}H_{39}N_5O_3$•0,5AcOH: C, 67,98; H, 7,55; N, 12,79, Encontrado: C, 68,01; H, 7,74; N, 12,77,

Ejemplo A(35): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2etil-6-metilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



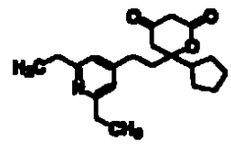
El compuesto del título se preparó de una forma análoga al ejemplo A(9) sustituyendo 2-etil-6metilpiridina en lugar de 2,6-bis-(2,2,2-trifluoro-etil)-piridina en la etapa 2 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,93 (d, J = 7,3 Hz, 3 H), 1,18-1,47 (m a, 8 H), 1,90 (m, 2 H), 2,15 (s, 3 H), 2,23-2,46 (m, 12 H), 2,56 (d, J = 16,9 Hz, 1H), 3,48 (d, J = 16,4 Hz, 1H), 3,61 (d, J = 16,2 Hz, 1H), 6,68 (s, 1H), 6,69 (s, 1H), 6,83 (s, 1H), 10,67 (s, 1H). MS (ESI): 490,20 $(M+H)^+$

Ejemplo A(36): 6-ciclopentil-6-[2-(2,6-dietilpiridin-4-il)etil]-4-hidroxi-3[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2 il)metil]-5,6-dihidro-2H-piran-2-ona



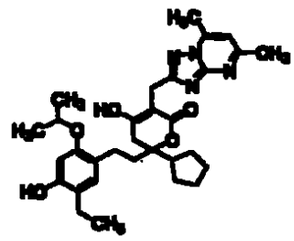
El compuesto del título se preparó de una forma análoga al ejemplo A(4) sustituyendo 6-ciclopentil-6-[2-(2etoxi-5-etil-4-hidroxi-fenil)-etil]-dihidro-piran-2,4-diona de la etapa 1 mostrada a continuación en lugar de 6-ciclopentil-6-[2-(2-etil-5-metoxi-piridin-4-il)-etil]-dihidro-piran-2,4-diona. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,93 (d, J = 7,3 Hz, 6 H), 1,11-1,46 (m a, 8 H), 1,87 (m, 2 H), 2,11 (s, 3 H), 2,21-2,33 (m, 4 H), 2,41 (d, J = 7,6 Hz, 4 H), 2,55 (d, J = 17,7 Hz, 1H), 3,48 (d, J = 16,2 Hz, 1H), 3,58 (d, J = 16,2 Hz, 1H), 6,68 (s, 2 H), 8,44 (s, 1H), 8,61 (s, 1H), 10,67 (s, 1H). Análisis calculado para $C_{28}H_{35}N_5O_3$•0,5AcOH: C, 67,03; H, 7,16; N, 13,48, Encontrado: C, 67,09; H, 7,25; N, 13,41.

Etapa 1: 6-ciclopentil-6-[2-(2,6-dietil-piridin-4-il)-etil]-dihidro-piran-2,4-diona



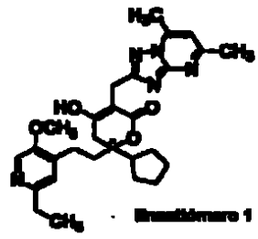
El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo 2,6-dietil-piridina de la etapa 1 del ejemplo A(17) en lugar de 4-bromo-2-etil-5-metoxi-piridina en la etapa 6 del ejemplo A(2). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,28 (t, J = 7,6 Hz, 6 H), 1,45-1,78 (m a, 10 H), 1,96 (m, 1H), 2,28 (m, 2 H), 2,65 (m, 2 H), 2,79 (q, J = 7,6 Hz, 4 H), 3,45 (m, 2 H), 6,81 (s, 2 H).

Ejemplo A(37): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2{5-etil-4-hidroxi-2-isopropoxifenil}etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



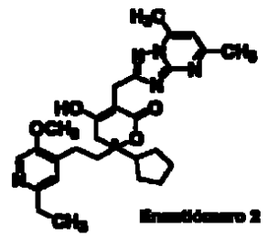
El compuesto del título se preparó de una forma análoga al ejemplo A(22) sustituyendo 2-yodopropano en lugar de yoduro de etilo en la etapa 1 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,06 (t, 1=7,3 Hz, 3 H), 1,23 (t, J = 6,1Hz, 3 H), 1,28 (t, J = 6,1Hz, 3 H), 1,46-1,95 (m a, 8 H), 1,95 (m, 1H), 2,11 (m, 1H), 2,39-2,64 (m, 12 H), 2,80 (d, J = 17,4 Hz, 1H), 3,76 (d, J = 15,9 Hz, 1H), 3,85 (d, J = 15,9 Hz, 1H), 4,40 (m, 1H), 6,44 (s, 1H), 6,77 (s, 1H), 7,09 (s, 1H), 8,99 (s, 1H), 10,95 (s, 1H). Análisis calculado para $C_{31}H_{40}N_4O_6$•0,3EtOAc: C, 67,25; H, 7,43; N, 9,74, Encontrado: C, 67,00; H, 7,44; N, 9,72.

Ejemplo A(38): Enantiómero 1 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2il)metil]4-[2-(2-etil-5-metoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



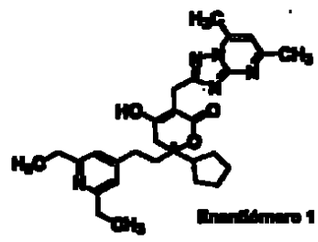
El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-metoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (75 mg, Ejemplo A(3)) usando HPLC quiral (Chiralpak AD-H, 140 bar, 35% MeOH). (21 mg, tiempo de retención 3,758 min, 100% ee)

Ejemplo A(39): Enantiómero 2 de 2 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2il)metil]-6-[2-(2-etil-5-metoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



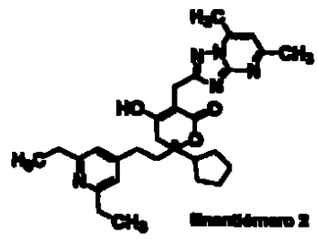
El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-metoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (75 mg, Ejemplo A(3)) usando HPLC quiral (Chiralpak AD-H, 140 bar, 35% MeOH). (21 mg, tiempo de retención 6,142 min, 100% ee)

Ejemplo A(40): Enantiómero 1 de 6-ciclopentil-6-[2-(2,6-dietilpiridin-4-il)etil]-3-[(5,7dimetil(1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



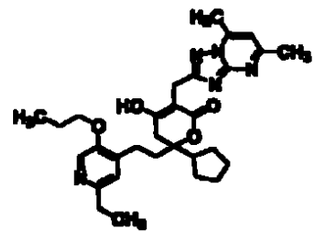
El compuesto del título se separó de la 6-ciclopentil-6-[2-(2,6-dietilpiridin-4il)etil]-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (60 mg, Ejemplo A(17)) usando HPLC quiral (Chiralpak AD-H, 140 bar, 35% MeOH). (12 mg, tiempo de retención 3,23 min, 100% ee)

Ejemplo A(41): Enantiómero 2 de 6-ciclopentil-6-[2-(2,6-dietilpiridin-4-il)etil]-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



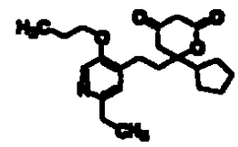
El compuesto del título se separó de la 6-ciclopentil-6-[2-(2,6-dietilpiridin-4-il)etil]-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2ona racémica (80 mg, Ejemplo A(17)) usando HPLC quiral (Chiralpak AD-H, 140 bar, 35% MeOH). (9 mg, tiempo de retención 6,46 min, 100% ee)

Ejemplo A(42): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-propoxipiridin-4-il)etil]-4hidroxi-5,6-dihidro-2H-piran-2-ona



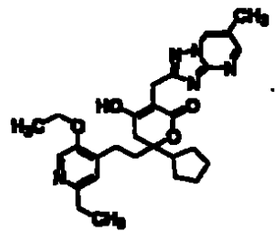
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 6-ciclopentil-6-[2-(2-etil-5-propoxi-piridin-4-il)-etil)-dihidro-piran-2,4-diona de la etapa 1 mostrada a continuación en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,06 (t, J = 7,3 Hz, 3 H), 1,26 (t, J = 7,6 Hz, 3 H), 1,51-1,87 (m a, 10 H), 2,25 (m, 2 H), 2,52-2,91 (m, 13 H), 3,84 (d, J = 16,2 Hz, 1H), 3,94 (d, J-16,2 Hz, 1H), 4,06 (t, J = 6,3 Hz, 2 H), 7,17 (s, 1H), 8,21 (s, 1H), 10,96 (s, 1H), 12,02 (s, 1H). Análisis calculado para $C_{30}H_{39}N_5O_4 \cdot 0{,}8H_2O$: C, 65,74; H, 7,47; N, 12,78, Encontrado: C, 65,68; H, 7,27; N, 12,80.

Etapa 1: 6-ciclopentil-6-[2-(2-etil-5-propoxi-piridin-4-il)-etil]-dihidro-piran-2,4-diona



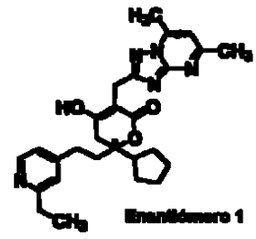
El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo 1-yodopropano en lugar de yoduro de metilo en la etapa 1 de ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,05 (t, J = 7,3 Hz, 3 H), 1,26 (t, J = 7,6 Hz, 3 H), 1,45-1,99 (m a, 12 H), 2,33 (m, 1H), 2,62-2,76 (m, 6 H), 3,43 (s, 2 H), 3,99 (t, J = 6,6 Hz, 2 H), 6,90 (s, 1H), 8,06 (s, 1H). Análisis calculado para $C_{22}H_{31}N=_4$•0,$_2H_2O$: C, 70,07; H, 8,39; N, 3,71, Encontrado: C, 70,10; H, 8,36; N, 3,34.

Ejemplo A(43): 6-ciclopentil-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5a]pirimidin-2 il)metil]-5,6-dihidro-2H-piran-2-ona



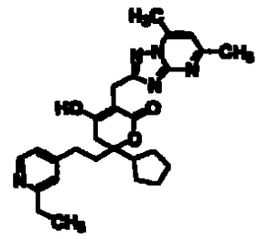
El compuesto del título se preparó de una forma análoga al ejemplo A(4) sustituyendo 6-ciclopentil-6-[2-(5etoxi-2-etil-piridin-4-il)-etil]-dihidro-piran-2,4-diona de la etapa 1 del ejemplo A(27) en lugar de 6-ciclopentil-6-[2-(2-etil-5-metoxi-piridin-4-il)-etil]-dihidro-piran-2,4-diona. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,21 (t, J = 7,3 Hz, 3 H), 1,34 (t, J = 7,6 Hz, 3 H), 1,42-1,79 (m a, 8 H), 2,09 (m, 2 H), 2,41-2,85 (m, 10 H), 3,78 (d, J = 16,2 Hz, 1H), 3,85 (d, J = 16,2 Hz, 1H), 4,11 (q, J = 7,6 Hz, 2 H), 7,12 (s, 1H), 8,15 (s, 1H), 8,74 (s, 1H), 8,96 (s, 1H), 10,94 (s, 1H). MS (ESI): 506,20 $(M+H)^+$

Ejemplo A(44): Enantiómero 1 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (60 mg, de la etapa 1 mostrada a continuación) usando HPLC quiral (Chiralpak AS-H, 100 bar, 60% MeOH). (28 mg, tiempo de retención 1,48 min, 100% ee)

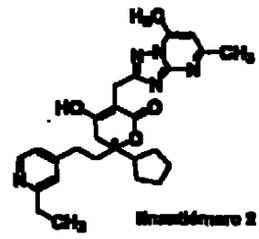
Etapa 1: 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(9) sustituyendo 2-etilpiridina en lugar de 2,6-bis-(2,2,2-trifluoro-etil)-piridina en la etapa 2 de ese ejemplo.

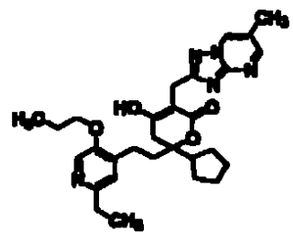
^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,24 (t, J = 7,6 Hz, 3 H), 1,44-1,75 (m a, 8 H), 2,2 (m, 2 H), 2,502,86 (m, 13 H), 3,76 (d, J = 16,0 Hz, 1H), 3,89 (d, J = 16,0 Hz, 1H), 7,11 (s, 1H), 7,18 (s, 2 H), 8,39 (s, 1H), 11,12 (s, 1H). MS (ESI): 476,25 $(M+H)^+$

Ejemplo A(45): Enantiómero 2 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (60 mg, de la etapa 1 del ejemplo A(44)) usando HPLC quiral (Chiralpak AS-H, 100 bar, MeOH al 60%). (21 mg, tiempo de retención 1,83 min, 98.4% ee)

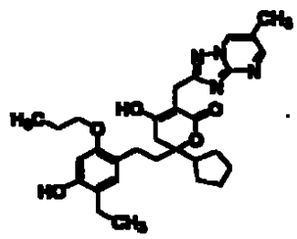
Ejemplo A(46): 6-ciclopentil-6-[2-(2-etil-5-propoxipiridin-4-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(4) sustituyendo 6-ciclopentil-6-[2-(2-etil-5-propoxi-piridin-4-il)-etil]-dihidro-piran-2,4-diona de la etapa 1 del ejemplo A(42) en lugar de 6-ciclopentil-6-(2-(2-etil-5-metoxipiridin-4-il)etil]dihidro-2H-piran-2,4(3H)diona.

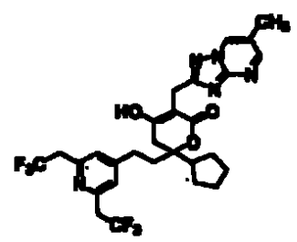
^{1}H RMN (400 MHz, DMSO-d_6) δ:11,20 (t, J = 7,3 Hz, 3 H), 1,40 (t, J = 7,3 Hz, 3 H), 1,61-1,96 (m a, 10 H), 2,29 (m, 2 H), 2,59 (s, 3 H), 2,60-2,90 (m, 6 H), 3,02 (d, J = 17,4 Hz, 1H), 3,97 (d, J = 15,9 Hz, 1H), 4,04 (d, J = 15,9 Hz, 1H), 4,20 (d, J = 6,3 Hz, 2 H), 7,30 (s, 1H), 8,34 (s, 1H), 8,93 (s, 1H), 9,14 (s, 1H), 11,16 (s, 1H). MS (ESI): 520,20 $(M+H)^+$

Ejemplo A(47): 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxifenil)etil]-4-hidroxi-3-[(6metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(4) sustituyendo 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona de la etapa 5 del ejemplo A(1) *mostrada a continuación* en lugar de 6-ciclopentil-6-[2-(2-etil-5-metoxipiridin-4-il)etil]dihidro-2H-piran-2,4(3H)diona. ^{1}H RMN (400 MHz, DMSO-d_6): δ 0,85(t, J = 7,3 Hz, 3 H), 0,92 (t, J = 7,6 Hz, 3 H), 1,27-1,60 (m, 10 H), 1,88 (m, 2 H), 2,25-2,44 (m, 9 H), 2,64 (d, J = 17,7 Hz, 1H), 3,66 (m, 4 H), 6,27 (s, 1H), 6,64 (s, 1H), 8,58 (s, 1H), 8,74 (s, 1H), 8,89 (s, 1H), 10,82 (s, 1H). Análisis calculado para $C_{30}H_{38}N_4O_5 \cdot 0,3H_2O$: C, 66,72; H, 7,20; N, 10,37, Encontrado: C, 66,55; H, 7,14; N, 10,39.

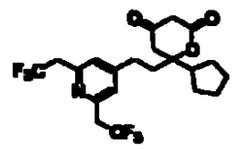
Ejemplo A(48): 6-(2-[2,6-Bis(2,2,2-trifluoroetil)piridin-4-il]etil)-6-ciclopentil-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(4) sustituyendo 6-ciclopentil-6-(2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona de la etapa 1 mostrada a continuación en lugar de 6-cydopentil-6-[2-(2-etil-5-metoxipiridin-4-il)etil]dihidro-2H-piran-2,4(3H)-diona. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,21-1,56 (m a, 8 H), 1,93 (m, 1H), 2,08 (m. 1H), 2,21 (s, 3 H), 2,24-2,58 (m, 4 H), 2,67 (d, J = 14,6 Hz, 1H), 3,56-3,72 (m, 6 H), 7,26 (s, 2 H), 8,53 (s, 1H), 8,81 (s, 1H), 10,83 (s, 1H). MS (ESI): 598,10 $(M+H)^+$

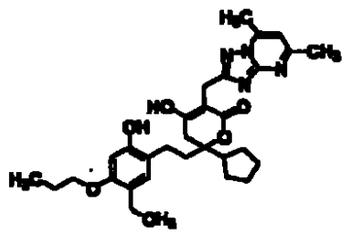
Etapa 1: 6-(2-[2,6-Bis-(2,2,2-trifluoro-etil)-piridin-4-il]-etil)-6-ciclopentil-dihidro-

piran-2,4diona



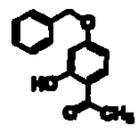
El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo 4-bromo-2,6-bis-(2,2,2-trifluoro-etil)-piridina de la etapa 5 del ejemplo A(9) en lugar de 4-bromo-2-etil-5-metoxi-piridina en la etapa 6 de ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,41-1,75 (m a, 8 H), 1,96 (m, 2 H), 2,28 (m, 1H), 2,70 (m, 4 H), 3,44-3,61 (m, 6 H), 7,10 (s, 2 H).

Ejemplo A(49): 6-ciclopentil-3-[(6,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etil-2-hidroxi-4-propoxifenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 6-ciclopentil-6-[2-(5etil-2-hidroxi-4-propoxi-fenil)-etil]-dihidro-piran-2,4-diona de la etapa 3 mostrada a continuación en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona. ^{1}H RMN (400 MHz, DMSO-d_6): δ 1,01 (m, 6 H), 1,42-1,77 (m, 10 H), 1,95 (m, 1H), 2,15 (m, 1H), 2,392,82 (m, 13 H), 3,70-3,84 (m, 4 H), 6,38 (s, 1H), 6,75 (s, 1H), 7,06 (s, 1H), 9,04 (s, 1H), 10,13 (s, 1H). MS (ESI): 549,20 $(M+H)^+$

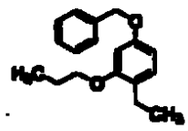
Etapa 1: 1-(4-benciloxi-2-hidroxi-fenil)-etanona



497
496

Se añadieron carbonato potásico (54 g, 0,39 mol) seguido de bromuro de bencilo (13,9 ml, 0,12 mol) a una solución de 2',4'-dihidroxiacetofenona (20 g, 0,13 mol) en DMF (180 ml). La mezcla se agitó durante 5 horas y después se repartió entre H_2O y EtOAc. La capa orgánica se lavó con $NaHCO_3$ saturado, HCl 1 N y salmuera, se secó sobre Na_2SO_4 y se concentró hasta un aceite transparente (23,7g, 81%). ^1H RMN (400 MHz, $CDCl_3$): δ 2,56 (s, 3 H),5,02 (s, 2 H), 6,51 (m, 2 H), 7,33-7,43 (m,5 H), 7,64 (d, J= 8,3 Hz, 1H), 12,73 (s, 1H).

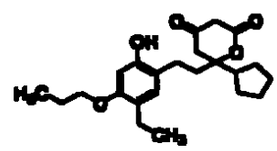
Etapa 2: 4-benciloxi-1-etil-2-propoxi-benceno



Se añadieron carbonato potásico (5,14 g, 12,4 mmol) seguido de 1-yodopropano (1,33 ml, 13,6 mmol) a una solución de 1-(4-benciloxi-2-hidroxi-fenil)-etanona (3 g, 12,4 mmol) en DMF (30 ml). La mezcla se agitó durante 15 horas y después se repartió entre H_2O y EtOAc. La capa orgánica se lavó con HCl 1 N, salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un sólido rosa. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-20% en hexanos) dio un sólido blanco (3,5 g, 99%).

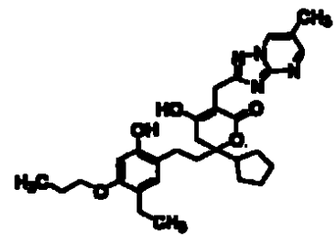
El sólido se suspendió en trietilenglicol (15 ml) y se trató con NaOH (1,23 g, 31 mmol) seguido de hidrazina monohidrato (1,79 ml, 37 mmol). La mezcla se calentó a 160 durante 16 horas. La mezcla de reacción se vertió en HCl 1 N y se extrajo con EtOAc. Los extractos orgánicos se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron hasta dar un aceite transparente. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-10% en hexanos) dio el compuesto del título en forma de un aceite transparente (2,5 g, 76%). ^1H RMN (400 MHz, $CDCl_3$): δ 1,04 (t, J = 7,3 Hz, 3 H), 1,16 (t, J = 7,6 Hz, 3 H), 1,80 (m, 2 H), 2,58 (q, J = 7,6 Hz, 2 H), 3,88 (t, J = 6,3 Hz, 2 H),5,03 (s, 2 H), 6,48 (dd, J = 8,1, 2,5 Hz, 1H), 6,51 (d, J = 2,3 Hz, 1H), 7,03 (d, J = 8,1Hz, 1H), 7,30-7,44 (m,5 H).

Etapa 3: 6-ciclopentil-6-[2-(5-etil-2-hidroxi-4-propoxi-fenil)-etil]-dihidro-piran-2,4-diona



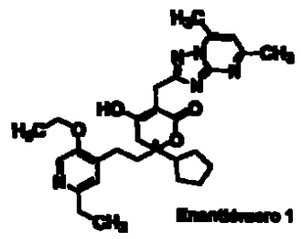
El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo 4-benciloxi-1-etil-2propoxi-benceno en lugar de 2-benciloxi-1-etil-4-propoxi-benceno en la etapa 3 de ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,03 (t, J = 7,6 Hz, 3 H), 1,18 (m, 6 H), 1,43-2,05 (m, 10 H), 2,50-2,82 (m, 6 H), 3,44 (m, 2 H), 3,84 (m, 2 H), 4,90 (s, 1H), 6,27 (s, 1H), 6,79 (s, 1H).

Ejemplo A(50): 6-ciclopentil-6-[2-(5-etil-2-hidroxi-4-propoxifenil)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona



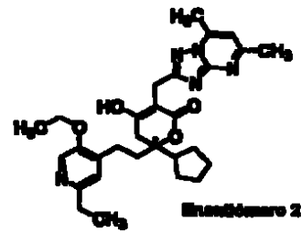
El compuesto del título se preparó de una forma análoga al ejemplo A(4) sustituyendo 6-ciclopentil-6-[2-(5etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona de la etapa 3 del ejemplo A(49) en lugar de 6-ciclopentil-6-[2-(2-etil-5-metoxipiridin-4-il)etil]dihidro-2H-piran-2,4(3H)diona. ^{1}H RMN (400 MHz, DMSO-d_6): δ 0,85 (m, 6 H), 1,25-1,62 (m, 10 H), 1,83 (m, 2 H), 2,19 (s, 3 H), 2,25-2,65 (m, 7 H), 3,61 (m, 2 H), 3,67 (t, J = 7,6 Hz, 2 H), 6,23 (s, 1H), 6,61 (s, 1H), 8,53 (s, 1H), 8,70 (s, 1H), 8,90 (s, 1H), 10,70 (s, 1H). MS (ESI): 535,20 $(M+H)^+$

Ejemplo A(51): Enantiómero 1 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2il)metil]-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



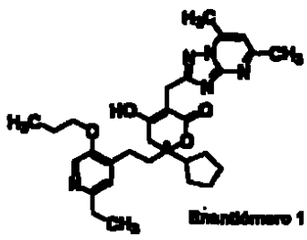
El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (85 mg, Ejemplo A(27)) usando HPLC quiral (Chiralpak AD-H, 140 bar, MeOH al 30%). (22 mg, tiempo de retención 5,38 min, 100% ee)

Ejemplo A(52): Enantiómero 2 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2il)metil]-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



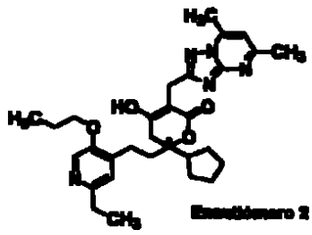
El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (85 mg, Ejemplo A(27)) usando HPLC quiral (Chiralpak AD-H, 140 bar, MeOH al 30%). (18 mg, tiempo de retención 7,21 min, 100% ee)

Ejemplo A(53): Enantiómero 1 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2il)metil]-6-[2-(2-etil-5-propoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



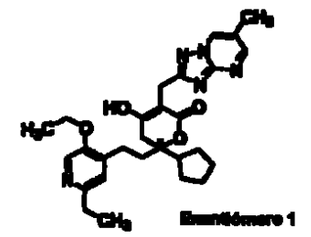
El compuesto del título se separó de la 6-ciclopentil-3-((5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-propoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona (80 mg, Ejemplo A(42)) usando HPLC quiral (Chiralpak AD-H, 140 bar, MeOH al 25% en peso/isopropilamina al 0,1%). (27 mg, tiempo de retención 6,91 min, 100% ee)

Ejemplo A(54): Enantiómero 2 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-propoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-propoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (80 mg, Ejemplo A(42)) usando HPLC quiral (Chiralpak AD-H, 140 bar, MeOH al 25% en peso/ isopropilamina al 0,1%). (12.3 mg, tiempo de retención 8,91 min, 100% ee)

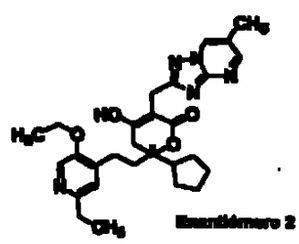
Ejemplo A(55): Enantiómero 1 de 6-ciclopentil-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona



El compuesto del título se separó de la 6-ciclopentil-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona racémica (33 mg, Ejemplo A(43)) usando HPLC quiral (Chiralpak AD-H, 140 bar,

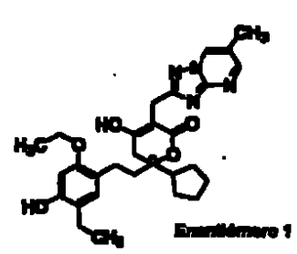
MeOH al 30%). (9 mg, tiempo de retención 5,49 min, 100% ee)

Ejemplo A(56): Enantiómero 2 de 6-ciclopentil-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona



El compuesto del título se separó de la 6-ciclopentil-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona racémica (33 mg, Ejemplo A(43)) usando HPLC quiral (Chiralpak AD-H, 140 bar, MeOH al 30%). (9.5 mg, tiempo de retención 6,79 min, 100% ee)

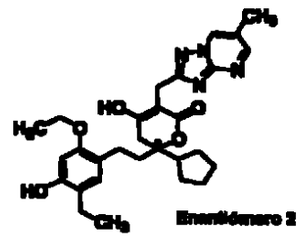
Ejemplo A(57): Enantiómero 1 de 6-ciclopentil-6-[2-(2-etoxi-5-etil-4-hidroxifenil)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona



El compuesto del título se separó de la 6-ciclopentil-6-[2-(2-etoxi-5-etil-4-hidroxifenil)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona racémica (70 mg, Ejemplo A(26)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 40% en peso/isopropilamina al 0,1%). (26 mg, tiempo de retención 1,73 min, 100% ee)

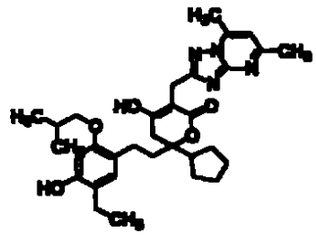
Ejemplo A(58): Enantiómero 2 de 6-ciclopentil-6-[2-(2-etoxi-5-etil-4-hidroxifenil)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-

dihidro-2H-piran-2-ona



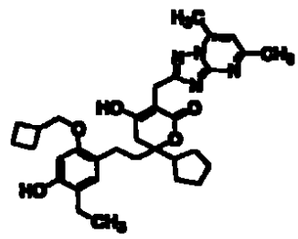
El compuesto del título se separó de la 6-ciclopentil-6-[2-(2-etoxi-5-etil-4-hidroxifenil)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona racémica (70 mg, Ejemplo A(26)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 40% en peso/isopropilamina al 0,1%). (27 mg, tiempo de retención 9,35 min, 100% ee)

Ejemplo A(59): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etil-4-hidroxi-2-isobutoxifenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



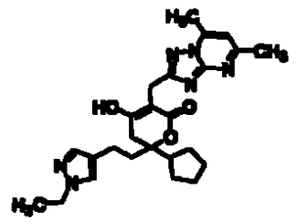
El compuesto del título se preparó de una forma análoga al ejemplo A(1), sustituyendo 1-yodo-2-metilpropano en lugar de 1-yodopropano en la etapa 1 de ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,00(d, J = 6,8 Hz, 6 H), 1,17(t, J = 7,6 Hz, 3 H), 1,35-1,78 (m, 12 H), 1,97 (t, J = 8,5 Hz, 2 H), 2,07 (m, 1H), 2,35-2,77 (m, 10 H), 3,61 (d, J = 6,3 Hz, 2 H), 4,04 (d, J = 15,4 Hz, 1H), 4,13 (d, J = 15,4 Hz, 1H), 6,30 (s, 1H), 6,82 (s, 1H), 6,84 (s, 1H), 10,72 (s, 1H).

Ejemplo A(60): 6-(2-[2-(ciclobutilmetoxi)-5-etil-4-hidroxifenil]etil)-6-ciclopentil-3-[(5,7dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil.4-hidroxi-5,6-dihidro-2H-piran-2-ona



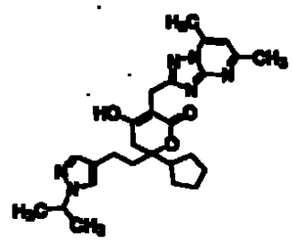
El compuesto del título se preparó de una forma análoga al ejemplo A(1), sustituyendo yodometilciclobutano en lugar de 1-yodopropano en la etapa 1 de ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,16 (t, J = 7,6 Hz, 3 H), 1,35-2,45 (m, 21H), 2,36-2,78 (m, 10 H), 3,83 (d, J = 6,5 Hz, 2 H), 4,07 (d, J = 15,4 Hz, 1H), 4,12 (d, J = 15,4 Hz, 1H), 6,31 (s, 1H), 6,81 (s, 1H), 6,84 (s, 1H), 10,72 (s, 1H).

Ejemplo A(61): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2 il)metil]-6-[2-(1-etil-1H-pirazol-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



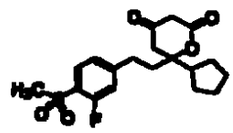
El compuesto del título se preparó de una forma análoga al ejemplo A(1), sustituyendo 1-etil-4-yodo-1H-pirazol (ref: Trofimenko, S. *J. Am. Chem Soc 88*,558,.1966) en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6): δ 1,36 (t, J = 7,4 Hz, 3 H), 1,57-1,89 (m 6 H), 2,10-2,16 (m, 2 H), 2,39-2,79 (m, 11H), 3,34 (m a, 2 H), 3,74 (d, J = 16,5 Hz, 1H), 3,85 (d, J = 16,5 Hz, 1H), 4,01-4,12 (m, 1H), 7,02 (s, 1H), 7,24 (s, 1H), 7,59 (s, 1H), 8,26 (s, 1H), 10,76 (s, 1H).

Ejemplo A(62): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-[2-(1-isopropil-1H-pirazol-4-il)etil]-5,6-dihidro-2H-piran-2-ona



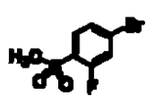
El compuesto del título se preparó de una forma análoga al ejemplo A(1)b, sustituyendo 4-yodo-1-isopropil-1H-pirazol (ref: Trofimenko, S. *J. Am. Chem Soc 88*,558, 1966) en lugar de 1benciloxi-2-etil-4-yodo-5-propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d6): δ 1,39 (d, J = 6,6 Hz, 6 H), 1,57-1,72(m, 6 H), 2,10-2,17 (m, 3 H), 2,39-2,79 (m, 11H), 3,74 (d, J = 16,2 Hz, 1H), 3,86 (d, J = 16,2 Hz, 1H), 4,42-4,48 (m, 1H), 7,00 (s, 1H), 7,23 (s, 1H), 7,56 (s, 1H), 8,23 (s, 1H), 10,74 (s, 1H).

Ejemplo A(63): 6-ciclopentil-4-{2-[3-fluoro-(metilsulfonil)fenil]etil}dihidro-2H-piran-2,4(3H)-diona



El compuesto del título se preparó de una forma análoga al ejemplo A(2), sustituyendo 4-bromo-2-fluoro-1-metanosulfonil-benceno de la etapa 1 mostrada a continuación en lugar de 4-bromo-2-etil-5-metoxipiridina en la etapa 6 de ese ejemplo. ^{1}H RMN ($CDCl_3$): δ 1,42-1,85 (m a, 8H), 1,97 (m, 2H), 2,29 (t, J = 7,6 Hz, 1H), 2,79 (m, 4H), 3,44 (s, 3H), 3,45 (s, 2H), 7,11 (s, 1H), 7,44 (m, 2 H)

Etapa 1: 4-Bromo-2-fluoro-1-rnetanosutfonil-benceno

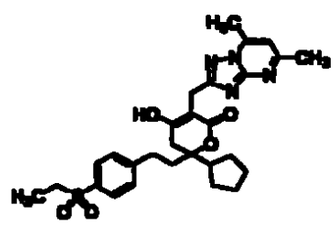


El compuesto del título se preparó de una forma análoga a la etapa 1 del ejemplo B(2), usando cloruro de 4-bromo-2-flubrobencenosulfonilo en lugar de cloruro de 4-bromo-2-clorobencenosulfonilo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,34 (s, 3 H), 7,57 (d, J =

505
504

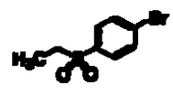
8,5, 2 H), 7,76 (d, J = 8,5 2 H), 8,14 (s, 1H)

Ejemplo A(64): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6(2-[4-(etilsulfonil)fenil]etil)-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(1), sustituyendo 1-bromo-4-etanosulfonil-benceno de la etapa 1 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,37 (t, J = 7,5 Hz, 3 H) 1,402,19 (m, 13 H), 2,58 (s, 3 H), 2,73 2,99(m, 7 H), 3,02 (q, J = 12,57 Hz, 2 H), 6,99 (s, 1H), 7,36 (dd, J = 3,56 Hz, 2 H), 7,70 (dd, J = 3,06 Hz, 1H). Análisis calculado para $C_{28}H_{34}N_4O_5S$: C, 62,43; H, 6,36; N, 10,40, Encontrado: C, 62,25; H, 6,40; N, 10,34.

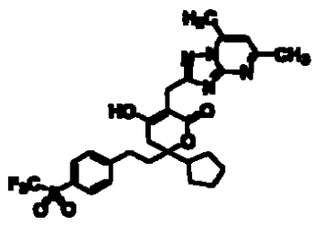
Etapa 1: Bromo-4-etanosulfonil-benceno



Se añadieron 1-Bromo-4-etilsulfanil-benceno (5,0 g) disuelto en ácido acético y permanganato potásico como una solución al 3% en agua (8 ml). La mezcla de reacción se calentó a 90°C durante 3 horas, tiempo después del cual la reacción se enfrió a temperatura ambiente y se repartió entre acetato de etilo y una solución de NaOH 2 N (500 ml de cada uno). Los extractos orgánicos se separaron y se lavaron con agua (100 ml), se secaron sobre sulfato sódico y se purificaron sobre una columna biotage eluyendo con 90:10 de hexanos : acetato de etilo para producir el compuesto del título en forma de un aceite transparente (2,70 g). ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,30 (t, J = 7,85 Hz, 3 H) 3,02 (q, J = 7,54 Hz, 2 H), 7,40 (m, 4 H).

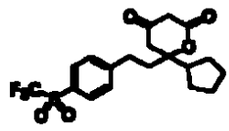
Ejemplo A(65): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-

hidroxi-6-(2-(4-[(trifluorometil)sulfonil]fenil)etil)-5,6-dihidro-2H-piran-2-ona



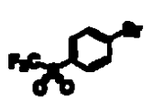
El compuesto del título se preparó de una forma análoga al ejemplo A(1), sustituyendo 6-ciclopentil-6-(2-[4-[(trifluorometil)sulfonil]fenil)etil)dihidro-2H-piran-2,4(3H)-diona (Ejemplo A(66) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona en ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,35-2,23 (m, 11H), 2,58 (s, 3 H), 2,73-2,89(m, 7 H), 3,03 (t, J = 8,57 Hz, 2 H), 6,99 (s, 1H), 7,78 (d, J = 2,56 Hz, 2 H), 8,10 (dd, J = 2,36 Hz, 2 H) Análisis calculado para $C_{27}H_{29}N_4O_5S$: C,56,04; H,5,05; N, 9,68, Encontrado: C,56,35; H,5,20; N, 9,34,

Ejemplo A(66): 6-ciclopentil-6-(2-(4-[(trifluorometil)sulfonil]fenil)etil)-dihidro-2H-piran-2,4(3H)-diona



El compuesto del título se preparó de una forma análoga al ejemplo A(2), sustituyendo 1-bromo-4-trifluorometanosulfonil-benceno de la etapa 1 mostrada a continuación en lugar de (4-bromo-2-etil-5metoxi-piridina en la etapa 6 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,35-2,33 (m, 11H), 2,803,15 (m, 6 H), 7,75 (d, J = 1,56 Hz, 2 H), 8,10 (d, J = 1,56 Hz, 2 H).

Etapa 1: 1-Bromo-4-trifluorometanosulfonil-benceno

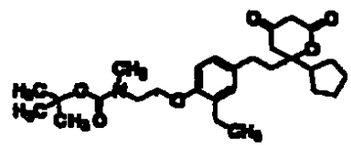


El compuesto del título se preparó de una forma análoga a la etapa 1 del ejem-

SO1
S06

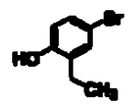
plo A(64), sustituyendo 1-bromo4-trifluorometilsulfanil-benceno en lugar de 1-bromo-4-etilsulfanil-benceno en la etapa 1 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): 5 7,80-7,93 (m, 4 H).

Ejemplo A(67): 2-(4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-etilfenoxi}etil(metil)carbamato de terc-butilo



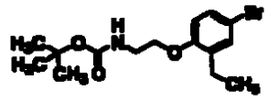
El compuesto del título se preparó de una forma análoga al ejemplo A(2), sustituyendo éster terc-butílico del ácido [2-(4-bromo-2-etil-fenoxi)etil]-metil-carbámico de la etapa 3 mostrada a continuación en lugar de 4-bromo-2etil-5-metoxi-piridina en la etapa 6 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,16 (t, J = 7,58 Hz, 3 H) 1,40-2,25 (m, 20 H), 2,62-3,13 (m, 14 H), 3,42 (q, J = 8,54 Hz, 2 H), 3,84 (t, J = 7,54 Hz, 2 H), 6,58 (d, J = 2,06 Hz, 1H), 6,66 (d, J = 1,58 Hz, 1H), 6,94 (s, 1H).

Etapa 1: 4-Bromo-2-etil-fenol



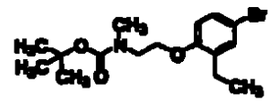
Se añadió una solución de tribromuro de tetrabutil amonio (39,56 g, 0,08 mol) en $CHCl_3$ (100 ml) a una solución agitada de 2-etil-fenol (10,0 g, 0,08 mol) disuelta en $CHCl_3$ (100 ml). La mezcla de reacción se agitó durante 2 horas y después se inactivó con una solución al 5% de tiosulfato sódico (100 ml). La mezcla bifásica se agitó durante 30 minutos y después las capas se separaron. La capa orgánica se lavó con HCl 1 N y salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un aceite rojo. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-15% en hexanos) dio el producto en forma de un aceite (14 g.). LCMS : APCI -VE=200 M/E.

Etapa 2: Éster terc-butílico del ácido [2-(4-bromo-2-etil-fenoxi)-etil]-carbámico



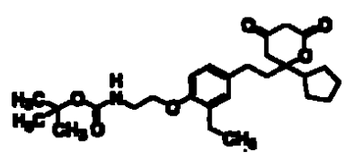
Se disolvió 4-bromo-2-etil-fenol (1,758, 8,70 mmol) de la etapa 1 anterior en acetonitrilo (10 ml) y se añadió carbonato de cesio (2,83g, 8,70 mmol) seguido de éster terc-butílico del ácido (2-bromo-etil)-carbámico (1,95 g, 8,70 mmol). La reacción se agitó a temperatura ambiente durante 18 horas. La mezcla se repartió entre acetato de etilo (200 ml) y agua (200 ml), los extractos orgánicos se separaron y se secaron sobre sulfato de magnesio y se concentraron hasta dar un aceite. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-30% en hexanos) dio el producto en forma de un aceite (1,0 g.). LCMS : APCI +VE=244 M/E, masa - BOC.

Etapa 3: Éster terc-butílico del ácido [2-(4-bromo-2-etil-fenoxi)-etil]-metil-carbámico



Se disolvió éster terc-butílico del ácido 2-(4-bromo-2-etil-fenoxi)-etil]-carbámico (1,0 g, 2,90 mmol) en THF (50 ml) y se añadió NaH al 60% (128 mg, 3,19 mmol) seguido de yoduro de metilo (0,2 ml, 3,19 mmol). La reacción se agitó a temperatura ambiente durante 18 horas. La mezcla se repartió entre acetato de etilo (100 ml) y agua (100 ml), los extractos orgánicos se separaron y se secaron sobre sulfato de magnesio y se concentraron hasta dar un aceite transparente. (1,3 g). LCMS : electronebulización +VE=380 M/E, masa + sodio.

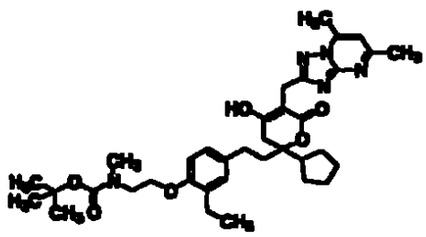
Ejemplo A(68): 2-(4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2 il)etil]-2-etilfenoxi)etilcarbamato de terc-butilo



El compuesto del título se preparó de una forma análoga al ejemplo A(2), susti-

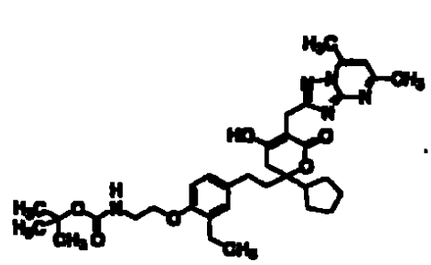
tuyendo éster terc-butílico del ácido (2-(4-bromo-2-etil-fenoxi)etil]carbámico de la etapa 2 del ejemplo A(67) en lugar de 4-bromo-2-etil-5-metoxi-piridina en la etapa 6 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,16 (t, J = 7,56 Hz, 3 H) 1,40-2,22 (m, 20 H), 2,60-3,10 (m, 11H), 3,39 (q, J = 8,54 Hz, 2 H), 3,84 (t, J = 7,54 Hz, 2 H), 6,56 (d, J = 2,06 Hz, 1H), 6,64 (d, J = 1,58 Hz, 1H), 6,94 (s, 1H).

Ejemplo A(69): 2-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-etilfenoxi]etil(metil)carbamato de terc-butilo



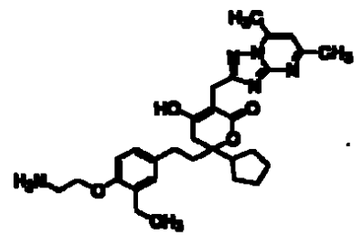
El compuesto del título se preparó de una forma análoga al ejemplo A(1), sustituyendo 2-[4-[2-(2ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-etilfenoxi]etil-(metil)carbamato de terc-butilo (Ejemplo A(67)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]dihidro-piran-2,4-diona en ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,20 (t, J = 8,56 Hz, 3 H) 1,40-2,30 (m, 20 H), 2,55-2,99 (m, 17 H), 3,35 (q, J = 9,54 Hz, 2 H), 3,90 (t, J = 7,54 Hz, 3 H), 6,60 (d, J = 1,56 Hz, 1H), 6,67 (d, J = 1,58 Hz, 1H), 7,00 (m, 2 H). Análisis calculado para $C_{38}H_{49}N_5O_6$: C, 66,74; H, 7,62; N, 10,81, Encontrado: C, 66,50; H, 7,40; N, 10,84.

Ejemplo A(70): 2-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-etilfenoxi]etilcarbamato de terc-butilo



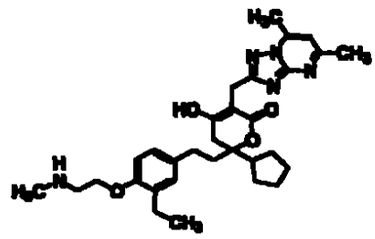
El compuesto del título se preparó de una forma análoga al ejemplo A(1), sustituyendo 2-[4-(2-(2ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-etilfenoxi)-etilcarbamato de terc-butilo (Ejemplo A(68)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidropiran-2,4-diona en ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,20 (t, J = 8,58 Hz, 3 H) 1,40-2,30 (m, 20 H), 2,55-2,99 (m, 15 H), 3,35 (q, J = 9,54 Hz, 2 H), 3,90 (t, J = 7,54 Hz, 3 H), 6,60 (d, J = 1,56 Hz, 1H), 6,67 (d, J = 1,56 Hz, 1H), 7,00 (m, 2 H). Análisis calculado para $C_{35}H_{47}N_5O_6$: C, 66,33; H,7,47; N, 11,05, Encontrado: C, 66,30; H, 7,40; N, 11,10.

Ejemplo A(71): 6-(2-[4-(2-Aminoetoxi)-3-etilfenil]etil)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



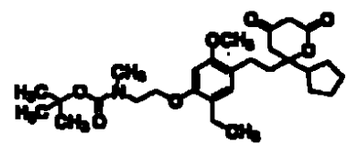
Se disolvió 2-[4-(2-[2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-etilfenoxi]-etilcarbamato de terc-butilo (Ejemplo A(70)) (250 mg) en HCl 4 N en dioxano (10 ml) y se agitó a temperatura ambiente durante 12 horas. Una vez completado, la mezcla se concentró y se destiló azeotrópicamente varias veces con diclorometano para producir el compuesto del título en forma de un sólido blanco (235 mg). ^{1}H RMN (300 MHz, MeOD): δ 1,18 (t, J = 7,56 Hz, 3 H) 1,32-2,35 (m, 11H), 2,58-2,85 (m, 15 H), 2,92 (dd, J = 16,54 Hz, 1H), 4,05 (t, J = 7,54 Hz, 2 H), 6,55 (d, J = 1,56 Hz, 1H), 6,65 (d, J = 1,56 Hz, 1H), 6,95 (s, 1H), 6,99 (s, 1H).

Ejemplo A(72): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(3etil-4-[2-(metilamino)etoxi]fenil)etil)-4-hidroxi-5,6-dihidro-2H-piran-2-ona



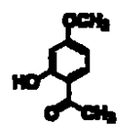
El compuesto del título se preparó de una forma análoga al ejemplo A(71) sustituyendo 2-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2Hpiran-2-il)etil)-2-etilfenoxi]etil(metil)carbamato de terc-butilo (Ejemplo A(69)) en lugar de 2-[4-(2-(2-cyctopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilfenoxi]etilcarbamato de terc-butilo en ese ejemplo. ^{1}H RMN (300 MHz, MeOD): δ 1,16 (t, J = 8,54 Hz, 3 H) 1,32-2,35 (m, 11H), 2,40 (s, 3H), 2,59-2,75 (m, 14 H), 2,92 (t, J = 16,54 Hz, 2 H), 3,84 (t, J = 7,54 Hz, 2 H), 6,55 (d, J = 2,08 Hz, 1H), 6,65 (d, J = 2,58 Hz, 1H), 6,95 (m, 2 H).

Ejemplo A(73): 2-(4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-etil-5-metoxifenoxi}etil(metil)carbamato de terc-butilo



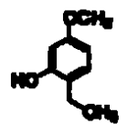
El compuesto del título se preparó de una forma análoga al ejemplo A(2), sustituyendo éster terc-butílico del ácido [2-(4-bromo-5-metoxi-2-etil-fenoxi)-etil]carbámico de la etapa 5 mostrada a continuación en lugar de 4-bromo-2-etil-5-metoxi-piridina en la etapa 6 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,16 (t, J = 7,56 Hz, 3 H) 1,40-2,25 (m, 20 H), 2,62-3,13 (m, 14 H), 3,42 (q, J = 8,54 Hz, 2 H), 3,84 (t, J = 7,54 Hz, 2 H), 4,00 (s, 3 H) 6,28 (s, 1H), 6,96 (s, 1H).

Etapa 1: 1-(4-Metoxi-2-hidroxi-fenil)-etanona



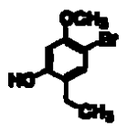
Se añadieron carbonato potásico (27,2 g, 197 mmol) seguido de yoduro de metilo (4,1 ml, 65,7 mmol) a una solución de 2',4'-dihidroxiacetofenona (10,0 g, 65,7 mmol) en DMF (100 ml). La mezcla se agitó durante 4 horas y después se repartió entre H_2O y EtOAc. La capa orgánica se lavó con $NaHCO_3$ saturado y salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un aceite transparente (11,0 g). ^1H RMN (300 MHz, $CDCl_3$): δ 2,60- (s, 3 H), 3,80 (s, 3 H), 6,40 (s, 1H) 6,51 (d, J = 2,45 Hz, 1H), 7,62 (d, J = 8,67 Hz, 1H), 12,90 (s, 1H).

Etapa 2: 5-Metoxi-2-etil-fenol



Se disolvió 1-(4-metoxi-2-hidroxi-fenil)-etanona (11,08) en MeOH (100 ml), se trató con Pd al 10%/C (4,08, tipo Degussa) y se agitó en un globo de H_2 durante 24 horas. La mezcla de reacción se filtró a través de una capa de celite lavando con EtOAc. El filtrado se concentró para dar el producto en forma de un aceite (10,0 g). ^1H RMN (300 MHz, $CDCl_3$): δ 1,20 (t, J = 7,85 Hz, 3 H) 2,60- (q, J = 6,22 Hz 2 H), 3,75 (s, 3 H), 6,40 (dd, J = 9,04 Hz, 2,64 Hz, 1H), 6,45 (d, J = 2,64 Hz, 1H) 7,00 (d, J = 8,29 Hz, 1H), 12,90 (s, 1H).

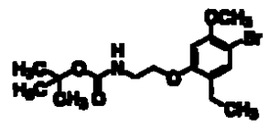
Etapa 3: 4-Bromo-5-metoxi-2-etil-fenol



Una solución de tribromuro de tetrabutil amonio (38,108, 79 mmol) en $CHCl_3$ (100 ml) se añadió a una solución agitada de 5-metoxi-2-etil-fenol (12,08, 79 mmol) disuelto en $CHCl_3$ (90 ml). La mezcla de reacción se agitó durante 4 horas y después se inactivó con una solución al 5% de tiosulfato sódico (90 ml). La mezcla bifásica se agitó durante 30 minutos y después las capas se separaron. La capa orgánica se lavó con HCl 1 N, salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un aceite rojo.

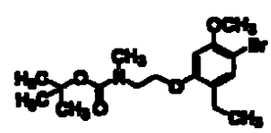
La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-60% en hexanos) dio el producto en forma de un aceite (19 g). LCMS : APCI -VE=230 M/E.

Etapa 4: Éster terc-butílico del ácido [2-(4-bromo-5-metoxi-2,etil-fenoxi)-etil]-carbámico



Se disolvió 4-bromo-5-metoxi-2-etil-fenol (10,09, 43 mmol) de la etapa 3 anterior en DMF (100 ml) y se añadió carbonato de cesio (21,17g, 65 mmol) seguido de éster terc-butílico del ácido (2-bromo-etil)-carbámico (21,178, 65 mmol). La reacción se agitó a temperatura ambiente durante 18 horas. La mezcla se repartió entre acetato de etilo (200 ml) y ácido cítrico al 10% (200 ml), los extractos orgánicos se separararon y se secaron sobre sulfato de magnesio y se concentraron hasta dar un aceite. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-30% en hexanos) dio el producto en forma de un aceite (10,0 g.). LCMS : APCI +VE=375 M/E.

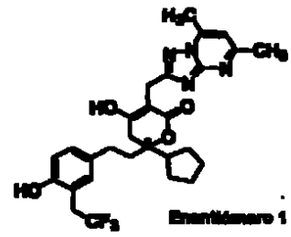
Etapa 5: Éster terc-butílico del ácido [2-(4-bromo-5-metoxi-2-etil-fenoxi)-etil]-metil-carbámico



Se disolvió éster terc-butílico del ácido 2-(4-bromo-5-metoxi-2-etil-fenoxi)-etil]-carbámico (5,0 g, 13,4 mmol) en THF (50 ml) y se añadió NaH al 60% (804 mg, 20,1 mmol) seguido de yoduro de metilo (1,3 ml, 20,1 mmol). La reacción se agitó a temperatura ambiente durante 18 horas. La mezcla se repartió entre acetato de etilo (100 ml) y ácido cítrico 1 N (100 ml), los extractos orgánicos se separaron y se secaron sobre sulfato de magnesio y se concentró hasta dar un aceite limpio. (6,0 g). LCMS : APCI +VE=389 M/E.

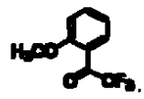
Ejemplo A(74): Enantiómero 1 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-

a]pirimidin-2-il)metil]-4-hidroxi-6-{2-[4-hidroxi-3-(2,2,2-trifluoroetil)fenil]-etil}-5,6-dihidro-2H-piran-2-ona



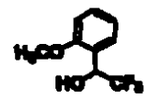
El compuesto del título se separó de la 6-ciclopentil3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-{2-[4-hidroxi-3-(2,2,2-trifluoroetil)fenil]etil}-5,6-dihidro-2H-piran-2-ona racémica (100 mg, de la etapa 9 mostrada a continuación) usando HPLC quiral (Chiralpak AS-H, 100 bar, MeOH al 30%). (26 mg, tiempo de retención 1,677 min, 100% ee)

Etapa 1: 2,2,2-trifluoro-1-(2-metoxifenil)etanona



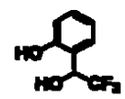
Se añadió lentamente bromuro de 2-metoxi fenil magnesio (35 ml) a una solución de trifluoroacetato de metilo (5,0 g) en éter dietílico (100 ml) a -78°C. La mezcla de reacción se calentó a temperatura ambiente durante 12 horas y se inactivó con una solución saturada de cloruro amónico (100 ml). La mezcla después se repartió entre acetato de etilo (500 ml) y agua (250 ml). Los extractos orgánicos se separaron y se secaron sobre sulfato de magnesio, se filtraron y se concentraron al vacío. El residuo bruto se purificó por cromatografía en columna sobre gel de sílice eluyendo con hexanos al 100% y 90:10 y 80:20 de hexanos:acetato de etilo, para producir el compuesto del título en forma de un aceite amarillo. (4,0 g). ^{1}H RMN ($CDCl_3$): δ 3,57 (s, 3H), 7,00 (m, 2H), 7,35 (m,1H), 7,63, (d, J = 2,54 Hz 2H).

Etapa 2: 2,2,2-trifluoro-1-(2-metoxifenil)etanol



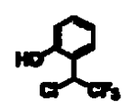
Se añadió paladio al 10% sobre carbono (1,5 g) a una solución de 2,2,2-trifluoro-1-(2metoxifenil)etanona (3,0 g) en metanol (50 ml). El producto resultante se hidrogenó a temperatura ambiente durante 12 horas. Después de este tiempo, el catalizador se retiró por filtración a través de una capa de celite y el disolvente se concentró al vacío. El producto bruto se purificó por cromatografía en columna sobre gel de sílice eluyendo con hexanos al 100% a 80:20 de hexanos:acetato de etilo para producir el compuesto del título en forma de un aceite amarillo (3,0 g). ^{1}H RMN ($CDCl_3$): δ 3,75 (d, J = 2,56 Hz, 1H), 3,96 (s, 3H),5,35 (m,1H), 7,05 (m, 2H), 7,50 (m,2H).

Etapa 3: 2-(2,2,2-trifluoro-1-hidroxietil)fenol



Se añadió tribromuro de boro (10 ml) (solución 1 M en DCM) a una solución de 2,2,2-trifluoro-1-(2metoxifenil)etanol (1,5 g) en diclorometano (20 ml). La mezcla de reacción se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 56 horas. La mezcla después se repartió entre DCM (100 ml) y HCl 1 N (100 ml), los extractos orgánicos se lavaron con agua (100 ml), se secaron sobre sulfato de magnesio, se filtraron y el disolvente se retiró al vacío para producir el compuesto del título en forma de un aceite amarillo transparente (1,5 g). ^{1}H RMN ($CDCl_3$): δ 3,50 (a a, 1H),5,25 (m, 1H), 6,73 (a a, 1H), 7,00 (m, 2H), 7,32 (d, J = 2,56 Hz, 1H), 7,45 (m, 1H).

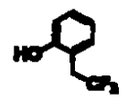
Etapa 4: 2-(1-cloro-2,2,2-trifluoroetil)fenol



Se añadió cloruro de tionilo (2,28 ml) a una solución de 2-(2,2,2-trifluoro-1-hidroxietil)fenol (3,0 g) y piridina (1,23 ml) en tolueno (50 ml). La reacción se agitó a temperatura ambiente durante 1 hora, tiempo después del cual el tolueno se retiró *al*

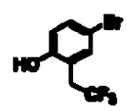
vacío y el residuo se repartió entre acetato de etilo (100 ml) y HCl 1 N (100 ml). Los extractos orgánicos se separaron y se secaron sobre sulfato de magnesio, se filtraron y el disolvente se retiró al vacío para producir el compuesto del título en forma de un aceite transparente (3,0 g). ^{1}H RMN ($CDCl_3$). δ 5,93 (m, 1H), 6,90 (d, J = 4,52 Hz, 1H), 7,10 (m, 1H), 7,35 (m, 1H), 7,69 (m, 1H).

Etapa 5: 2-(2,2,2-trifluoroetil)fenol



Se añadió borohidruro sódico (.930 g) a una solución de 2-(1-cloro-2,2,2-trifluoroetil)fenol (2,6 g) en THF (30 ml). La mezcla de reacción después se agitó durante 14 horas a temperatura ambiente en una atmósfera de nitrógeno, tiempo después del cual la reacción se interrumpió con HCl 1 N (50 ml) y se repartió entre HCl 1 N (100 ml) y acetato de etilo (200 ml), los extractos orgánicos se separaron y se secaron sobre sulfato de magnesio, se filtraron y el disolvente se evaporó *al vacío* para producir el compuesto del título en forma de un semi sólido(2,4 g). ^{1}H RMN ($CDCl_3$): δ 3,50 (q, J = 21,08 Hz, 2H), 6,80 (m, 1H), 7,00 (m, 1H), 7,25 (m, 2H).

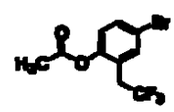
Etapa 6: 4-bromo-2-(2,2,2-trifluoroetil)fenol



Se disolvió tribromuro de tetrabutilamonio (6,56 g) en cloroformo (50 ml) y se añadió gota a gota a una solución de 2-(2,2,2-trifuoroetil)fenol (2,4 g) en cloroformo (50 ml). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas, tiempo después del cual se añadió una solución de tiosulfato sódico al 5% (100 ml) y el producto resultante se agitó durante 30 minutos. La mezcla después se repartió entre diclorometano (100 ml) y HCl 1 N (200 ml). Los extractos orgánicos se separaron y se secaron sobre sulfato de magnesio. El disolvente después se retiró al vacío, después el residuo bruto se purificó por cromatografía en columna sobre gel de sílice eluyendo con 90:10 de hexanos :acetato de etilo para producir el compuesto del título en forma

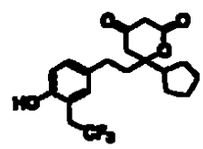
de un aceite amarillo (3,24 g). ^{1}H RMN ($CDCl_3$): δ 3,50 (q, J = 21,48 Hz 2H), 6,70 (d, J = 2,54 Hz, 1H), 7,32 (d, J = 2,54 Hz, 1H), 7,45 (s, 1H).

Etapa 7: 4-bromo-2-(2,2,2-trifluoro-etil)-fenil éster del ácido acético



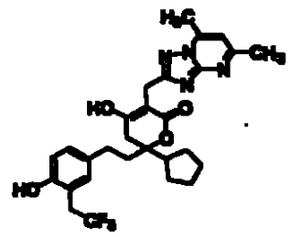
Se añadieron cloruro de acetilo (0,91 ml, 12,8 mmol) seguido de trietilamina (1,8 ml, 12,8 mmol) a una solución agitada de 4-bromo-2-(2,2,2-trifluoroetil)fenol (2,55 g, 10,7 mmol) disuelta en CH_2Cl_3 (20 ml). La reacción se agitó durante 45 minutos y después se repartió entre HCl 1 N y EtOAc. La capa orgánica se lavó con $NaHCO_3$ saturado y salmuera, se secó sobre Na_2SO_4 y se concentró. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-20% en hexanos) dio el producto en forma de un aceite transparente (2,50g). LCMS : APCI 297 MH+

Etapa 8: 6-ciclopentil-6-(2-(4-hidroxi-3-(2,2,2-trifluoroetil)fenil]etil)dihidro-2H-piran2,4(3H).diona



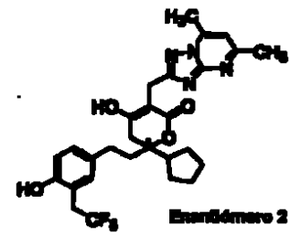
El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo 4-bromo-2(2,2,2-trifluoro-etil)-fenil éster del ácido acético de la etapa 7 anterior en lugar de 4-bromo-2-etil-5-metoxi-piridina en la etapa 6 de ese ejemplo. ^{1}H RMN ($CDCl_3$): δ 1,35-1,70 (m a, 6H), 1,93, (m a, 2H), 2,04-2,21 (m a, 3H), 2,83-3,12 (m a, 8H), 6,78 (dd, J = 2,81Hz 2H), 6,99 (s, 1H). MS (APCI): 385 (MH).

Etapa 9: 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-(2-[4-hidroxi-3-(2,2,2-trifluoroetil)fenil]etil)-5,6-dihidro-2H-piran-2-ona



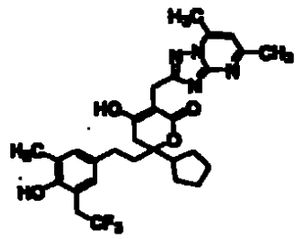
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo.6-ciclopentil-6-[2-[4-hidroxi-3-(2,2,2-trifluoroetil)fenil]etil)dihidro-2H-piran-2,4(3H)-diona en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona en ese ejemplo. ^{1}H RMN (DMSO): δ 1,40-1,90 (m a, 8H), 1,99-2,28 (m a, 3H), 2,58 (s, 3H), 2,73 (m,5H), 3,00 (m, 2H); 3,10 (m, 2H), 3,47 (m, 3H), 6,79 (m, 2H), 7,05 (m, 2H), 8,83 (s a, 1H), 10,0 (s a, 1H). Análisis calculado para $C_{28}H_{31}O_4N_4F_3$: C, 61,76; H,5,74, N, 10,29, Encontrado: C, 61,50; H,5,50, N, 10,14.

Ejemplo A(75): Enantiómero 2 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-(2-[4-hidroxi.3-(2,2,2-trifluoroetil)fenil]-etil}-5,6-dihidro-2H-piran-2-ona



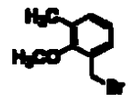
El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-dimetil(1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-[2-[4-hidroxi-3-(2,2,2-trifluoroetil)fenil]etil]-5,6-dihidro-2H-piran-2-ona racémica (100 mg, de la etapa 9 del ejemplo A(74) usando HPLC quiral (Chiralpak AS-H, 100 bar, MeOH al 30%). (27 mg, tiempo de retención 3,566 min, 100% ee)

Ejemplo A(76): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-[2-[4-hidroxi-3-metil-5-(2,2,2-trifluoroetil)fenil]-etil)-5,6-dihidro-2H-piran-2ona



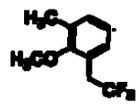
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 2-benciloxi-5-yodo-1-metil-3-(2,2,2-trifluoro-etil)-benceno de la etapa 5 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,35-1,80 (m, 8 H), 2,00-2,40 (m, 6 H), 2,58 (s, 3 H), 2,80 (m, 7 H), 3,10 (t, J = 7,06 Hz, 2 H), 3,20 (q, J = 10,47 Hz, 2 H) 6,52 (s, 1H), 6,81 (s, 1H), 6,99 (s, 1H), 8,82 (s, 2H). Análisis calculado para $C_{29}H_{33}F_3N_4O_4$: C, 62,36; H,5,95; N, 10,03, Encontrado: C, 62,30; H,5,83; N, 10,16.

Etapa 1: 1-Bromometil-2-metoxi-3-metil-benceno



Se disolvió 2-5-dimetilanisol (10,08, 73 mmol) en CCl_4 (100 ml) y se añadieron NBS (26,26 g, 147 mmol) seguido de peróxido de benzoílo (884 mg,5% en moles). La reacción se calentó a reflujo y se agitó a esa temperatura durante 48 horas, tiempo después del cual la mezcla se enfrió a temperatura ambiente y se filtró. El filtrado se concentró y se purificó por cromatografía en columna ultrarrápida (EtOAc al 0%-30% en hexanos) para dar el producto en forma de un sólido blanco (19,3g.). LCMS: APCI - VE=213

Etapa 2: 2-Metoxi-1-metil-3-(2,2,2-trifluoro-etil)-benceno

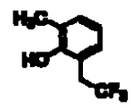


Se añadió trimetil(trifluorometil)silano (25,39 ml, 162,5 mmol) a una mezcla agitada de 1bromometil-2-metoxi-3-metil-benceno (19 g, 65 mmol), KF (9,44 g, 162,5

526
519

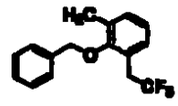
mmol), CuI (37,10 g, 195 mmol) en DMF (75 ml) y NMP (75 ml). La mezcla de reacción se calentó a 55°C en una atmósfera de N_2 durante 15 horas. La mezcla se vertió en agua, se basificó con NaOH 1 N y se extrajo con EtOAc. Las capas orgánicas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron hasta dar un aceite negro. La cromatografía en columna ultrarrápida (EtOAc al 0%-80% en hexanos) dio el producto en forma de un aceite amarillo (12,0 g). LCMS: APCI VE=203

Etapa 3: 2-metil-6-(2,2,2-trifluoro-etil)-fenol



Se disolvió 2-metoxi-1-metil-3-(2,2,2-trifluoro-etil)-benceno (6,0 g) en diclorometano (100 ml) y se añadió BBr_3 (100 ml). La reacción se dejó en agitación a temperatura ambiente durante 12 horas, tiempo después del cual se interrumpió lentamente con HCl concentrado. Después, la mezcla se basificó con una solución de NaOH 2 N y los orgánicos se desecharon. La capa acuosa se acidificó con HCl 1 N y el producto se extrajo con acetato de etilo para producir el compuesto del título en forma de un aceite de color pardo (4,43 g). LCMS: APCI - VE=189

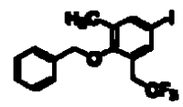
Etapa 4: 2-benciloxi-1-metil-3-(2,2,2-trifluoro-etil)-benceno



Se añadieron carbonato potásico (953 mg, 6,89 mmol) seguido de bromuro de bencilo (0,8 ml, 6,89 mmol) a una solución de 2-metil-6-(2,2,2-trifluoro-etil)-fenol (1,78 g, 6,89 mmol) en DMF (20 ml). La mezcla se agitó a temperatura ambiente durante 15 horas y después se repartió entre H_2O y EtOAc. La capa orgánica se lavó con HCl 1 N y salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un aceite de color pardo. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-20% en hexanos) dio el producto en forma de un aceite transparente (2,1 g). LCMS: APCI -VE=279

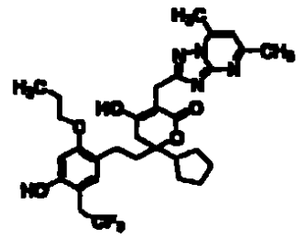
Etapa 5: 2-benciloxi-5-yodo-1-metil-3-(2,2,2-trifluoro-etil)-benceno

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520



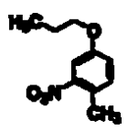
Una solución de yodo (1,52 g, 6,0 mmol) disuelta en $CHCl_3$ (80 ml) se añadió gota a gota a una mezcla agitada de 2-benciloxi-1-metil-3-(2,2,2-trifluoro-etil)-benceno (2,19, 6,0 mmol) y trifluoroacetato de plata (1,33g, 6,0 mmol) en $CHCl_3$ (20 ml). Después de completarse la adición, la mezcla de reacción se agitó durante 1 hora. La mezcla se filtró a través de una capa de celite lavando con CH_2Cl_2. El filtrado se lavó con $Na_2S_2O_3$ saturado y salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un sólido amarillo pálido (1,68g). LCMS: APCI -VE=405

Ejemplo A(77): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-(2-[4-hidroxi-2-propoxi-5-(2,2,2-trifluoroetil)fenil]-etil}-5,6-ihidro-2H-piran2-ona



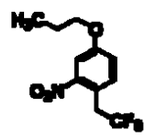
El compuesto del título se preparó de una forma análoga al ejemplo A(1), sustituyendo 1-benciloxi-4-yodo-5-propoxi-2-(2,2,2-trifluoro-etil)-benceno de la etapa 4 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en la etapa 4 de ese ejemplo. ^1H RMN (300 MHz, $CDCl_3$): δ 0,98 (t, J = 6,7£ Hz, 3 H) 1,40-2,40 (m, 10 H), 2,50-2,75 (m, 10 H), 3,10 (q, J = 10,06 Hz, 2 H), 3,78 (t, J = 8,56 Hz, 2 H; 6,12 (s, 1H), 6,99 (m, 2 H), 10,12 (s a, 1H). Análisis calculado para $C_{31}H_{37}F_3N_4O_6$: C, 61,73; H, 6,19; N, 9,29, Encontrado: C, 61,60; H, 6,24; N, 9,39.

Etapa 1: 1-metil-2-nitro-4-propoxi-benceno



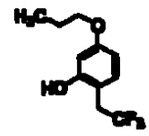
Se añadieron carbonato potásico (13,5 g, 0,098 mol) seguido de 1-yodopropano (9,58 ml, 0,098 mol) a una solución de 4-metil-3-nitro-fenol (15 g, 0,098 mol) en DMF (100 ml). La mezcla se agitó durante 5 horas y después se repartió entre H_20 y EtOAc. La capa orgánica se lavó con $NaHCO_3$ saturado y salmuera, se secó sobre Na_2SO_4 y se concentró hasta un aceite transparente (17,5 g).

Etapa 2: 2-Nitro-4-propoxi-1-(2,2,2-trifluoro-etil)-benceno



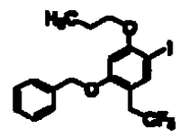
Se disolvió 1-metil-2-nitro-4-propoxi-benceno (17,0 g, 87 mmol) en CCl4 (100 ml) y se añadieron NBS (15,58g, 87 mmol) seguido de peróxido de benzoílo (1,0 mg,5% en moles). La reacción se calentó a reflujo y se agitó a esa temperatura durante 24 horas, tiempo después del cual la mezcla se enfrió a temperatura ambiente y se filtró. E filtrado se concentró y se purificó por cromatografía en columna ultrarrápida (EtOAc al 0%-5% en hexanos) para dar el bromuro en forma de un sólido blanco (7,0 g). Se añadió trimetil(trifluorometil)silano (4,8 ml, 31,9 mmol) a una mezcla agitada del bromuro (7,0 g, 25,5 mmol), KF (1,85 g, 31,90 mmol), CuI (7,28g, 38,25 mmol) en DMF (50 ml) y NMP (50 ml). La mezcla de reacción se calentó a 55°C en una atmósfera de N_2 durante 15 horas. La mezcla se vertió en agua, se basificó con NaOH 1 N y se extrajo con EtOAc. Las capas orgánicas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron hasta dar un aceite negro que se purificó por cromatografía en columna ultrarrápida (EtOAc al 0%-10% en hexanos) para dar el producto en forma de un aceite amarillo (3,0 g). ^1H RMN (300 MHz, $CDCl_3$): δ 1,06 (t, J = 6,79 Hz, 3 H) 1,80 (m, 2 H), 3,68 (q, J = 10,47 Hz, 2 H), 3,78 (t, J = 8,56 Hz, 2 H) 6,76 (d, J = 2,33 Hz, 1H) 7,33 (d, J = 2,33 Hz, 1H), 7,69 (s, 1H).

Etapa 3: 5-Propoxi-2-(2,2,2-trifluoro-etil)-fenol



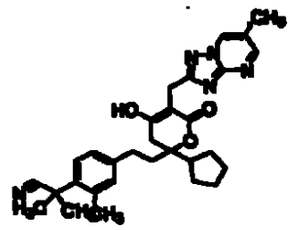
Se disolvió 2-nitro-4-propoxi-1-(2,2,2-trifluoro-etil)-benceno (3,0 g) en etanol (50 ml) y se añadió paladio al 10% sobre carbono (1,0 g). La mezcla se hidrogenó mediante el uso de un globo durante 5 horas, tiempo después del cual el catalizador se retiró por filtración a través de una capa de celite. El filtrado se concentró y se purificó por cromatografía en columna ultrarrápida (EtOAc al 0%-60% en hexanos) para dar la anilina en forma de un aceite amarillo (2,5 g). Esta anilina se suspendió en H_2SO_4 (2,05 ml en 5 ml de agua) y se enfrió a -5°C. Se añadió gota a gota nitrito sódico (814 mg en 5 ml de agua). La mezcla se agitó a 0°C durante 30 minutos más y después la mezcla se añadió a una solución de ácido sulfúrico (19 ml en agua 100 ml). La mezcla se calentó a 80°C durante 1 hora. La mezcla de reacción se enfrió a temperatura ambiente y el producto se extrajo usando acetato de etilo. Los extractos orgánicos se separaron y se secaron sobre sulfato de magnesio y el disolvente se concentró. El residuo se purificó por cromatografía en columna ultrarrápida (EtOAc al 0%-60% en hexanos) para producir el producto en forma de un sólido rojo (500 mg). ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,06 (t, J = 6,79 Hz, 3 H) 1,80 (m, 2 H), 3,46 (q, J = 10,33 Hz, 2 H), 3,92 (t, J = 8,86 Hz, 2 H) 6,26 (d, J = 2,33 Hz, 1H) 6,48 (s, 1H) 7,10 (d, J = 2,33 Hz, 1H), 8,40 (s a, 1H).

Etapa 4: 1-benciloxi-4-yodo-5-propoxi-2-(2,2,2-trifluoro-etil)-benceno



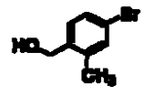
El compuesto del título se preparó de una forma análoga al ejemplo A(76) sustituyendo 5-propoxi-2-(2,2,2-trifluoro-etil)-fenol de la etapa 3 anterior en lugar de 2-metil-6-(2,2,2-trifluoro-etil)fenol en la etapa 4 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,06 (t, J = 6,79 Hz, 3 H) 1,80 (m, 2 H), 3,46 (q, J = 10,56 Hz, 2 H), 4,00 (t, J = 8,56 Hz, 2 H) 4,99 (s, 2 H), 6,65 (s, 1H) 7,26-7,42 (m, 6 H).

Ejemplo A(78): 2-[4-(2-(2-ciclopentil-4-hidroxi-5-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-oxo-3,6,dihidro-2H-piran-2-il}etil)-2-metilfenil]-2-metilpropanonitrilo



Se añadió 6-metil-[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído (0,11 g, 0,7 mmol) a una solución de 2-{4-[2-(2-ciclopentil-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)-etil]-2-metil-fenil}2-metil-propionitrilo (0,16 g, 0,5 mmol, de la etapa 5 mostrada a continuación) en MeOH (4 ml). La mezcla de reacción se agitó durante 15 minutos y después se trató con complejo de borano-dietilamina (34 mg, 0,6 mmol). Después de 15 horas, la mezcla de reacción se filtró a través de una frita de vidrio lavando con MeOH. El filtrado se concentró hasta dar un aceite amarillo. La purificación por HPLC preparativa dio el producto en forma de un polvo blanco (32 mg, 14% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6): δ.35-1,46 (2 H, m) 1,75 (6 H, s) 1,77-1,81 (2 H, m) 1,93-2,04 (3 H, m) 2,35-2,46 (2 H, m) 2,48 (3 H, s) 2,52-2,56 (2 H, m) 2,59 (3 H, s) 2,61-2,78 (4 H, m) 4,10 (2 H, d, J = 8,08 Hz) 6,96-7,02 (2 H, m) 7,15-7,23 (1H, m) 8,57-8,63 (1H, m) 8,69 (1H, d, J=2,53 Hz). MS (ESI): 512 (M-H).

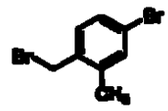
Etapa 1: (4-Bromo-2-metil-fenil)-metanol



Se disolvió ácido 4-bromo-2-metil-benzoico (9,88 g, 45,9 mmol) en THF (100 ml) y la solución se enfrió a 0°C. A esta solución se le añadió una solución de BH_3THF 1 M (91,89 ml, 91,89 mmol) a 0°C y la solución se agitó vigorosamente durante 3 horas a temperatura ambiente. La mezcla de reacción se diluyó con agua fría (20 ml), se lavó con una solución saturada de $NaHCO_3$ y después se extrajo 3 veces con éter (300 ml). El éter orgánico combinado se lavó con salmuera (250 ml), se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se purificó mediante cromatografía en columna ultrarrápida (EtOAc al 25%-55% en hexano) para dar un sólido blanco (8,24 g, 90% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ: 2,32 (2 H, s) 4,64 (1H, d, J = 5,81Hz) 7,20 - 7,26 (2 H, m) 7,30 - 7,36 (1H. m).

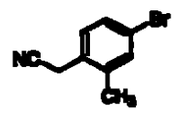
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Etapa 2: 4-Bromo-1 -bromometil-2-metil-benceno



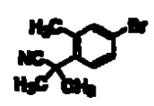
Se añadieron trifenilfosfina (11,35 g, 43,27 mmol) seguido de tetrabromuro de carbono (14,35 g, 43,27 mmol) a una solución de (4-bromo-2-metil-fenil)-metanol (7,25 g, 36 mmol) en CH_2Cl_2 (200 ml). La mezcla se agitó a temperatura ambiente durante 5 horas. La solución se concentró hasta 15 ml. El residuo se purificó por cromatografía en columna ultrarrápida (EtOAc al 1%-10% en hexano) dando el producto en forma de un aceite pardo (9,25 g, 81% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ: 2,39 (3 H, s) 4,45 (2 H, s) 7,17 (1H, d, J = 8,08 Hz) 7,29 (2 H, m) 7,30 (1H, dd, J = 8,08, 2,02 Hz) 7,34 (1H, s).

Etapa 3: (4-Bromo-2-metil-fenil)-acetonitrilo



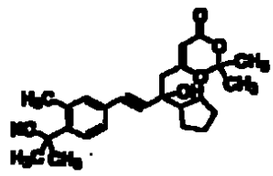
A una solución de 4-bromo-1-bromometil-2-metil-benceno (3,96 g, 15 mmol) disuelto en DMF (16 ml) se le añadieron cianuro sódico (0,85 g, 17,25 mmol) y agua (1,8 ml). La reacción se agitó durante una noche a temperatura ambiente. A la reacción se le añadieron 100 ml de agua; 80 ml de $NaHCO_3$ saturado y 100 ml de EtOAc. Las capas se separaron y la capa acuosa se extrajo con 3 x 100 ml de EtOAc. Los extractos orgánicos combinados se lavaron con 100 ml agua y después se secaron sobre Na_2SO_4. Después de retirar por filtración los sólidos, las aguas madre se concentraron hasta obtener el producto deseado por evaporación rotatoria (2,92 g, 92,7% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$): δ 2,32 (2 H, s), 3,62 (1H, s), 7,20-7,27 (1H, m), 7,32-7,41 (1H, m).

Etapa 4: 2-(4-Bromo-2-metil-fenil)-2-metil-propionitrilo



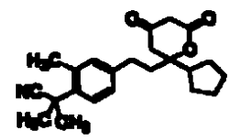
A una solución de (4-bromo-2-metil-fenil)-acetonitrilo (1,26 g, 6 mmol) de la etapa 3 anterior en DMF (15 ml) enfriada a -10°C se le añadió t-butóxido potásico (1,62 g, 14,4 mmol). La reacción se agitó durante 15 minutos y se añadió lentamente yodometano (0,86 ml, 13,8 mmol). La reacción se agitó durante 2 horas y después e interrumpió con HOAc (0,51 ml, 9 mmol). La mezcla de reacción se agitó durante 20 minutos y se mezcló con IPE (250 ml) y agua (200 ml). Las capas se separaron y la capa acuosa se extrajo 3 veces con 100 ml de IPE. Los extractos orgánicos combinados se lavaron con 200 ml de agua y después se secaron sobre $MgSO_4$. Después de retirar los sólidos por filtración, las aguas madre se concentraron hasta dar el producto bruto por evaporación rotatoria. El residuo se purificó por cromatografía en columna ultrarrápida (EtOAc al 0%-75%en hexano) para dar el producto deseado. Rendimiento: 1,28 g, 89%. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,77 (6 H, s) 2,62 (3 H, s) 7,16 (1H, d, J = 8,59 Hz) 7,31 - 7,40 (2 H, m).

Etapa 6: 2-(4-(2-[2-ciclopentil-4-hidroxi-6-(6-metil-[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil)-6-oxo-3,6-dihidro-2H-piran-2-il]-etil)-2-metil-fenil)-2-metil-propionitrilo



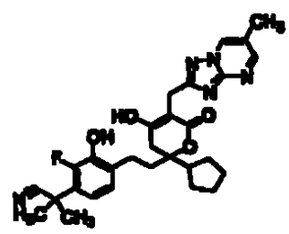
Una mezcla de 2-(4-bromo-2-metil-fenil)-2-metil-propionitrilo (1,24 g,5,2 mmol), 6-(2-ciclopentil-2-hidroxibut-3-inil)-2,2-dimetil-4H-1,3-dioxin-4-ona (1,37 g,5,2 mmol), $PdCl_2(PPh_3)_2$ (0,13 g, 4% en moles) y CuI (7,9 mg, 8% en moles) en diisopropilamina (4 ml) y DMF (8 ml) se calentó a 90°C durante 40 min. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con EtOAc (250 ml), después se lavó con NH_4Cl acuoso y salmuera y se secó sobre Na_2SO_4. El disolvente se retiró al vacío y el residuo se purificó por cromatografía en columna ultrarrápida para dar el producto deseado. Rendimiento: 1,28 g,57%. ^{1}H RMN (400 MHz, $CDCl_3$) δ: 1,38-1,40 (1H, m) 1,52 - 1,62 (6 H, m) 1,65 - 1,71 (7 H, m) 1,92 - 1,99 (2 H, m) 2,33 - 2,42 (2 H, m) 2,53 (3 H, s) 2,56 - 2,67 (3 H, m) 5,43 (1H, s) 6,95 - 7,04 (2 H, m) 7,22 (1H, d, J = 8,08 Hz). MS (ESI): 420 (M-H).

Etapa 6: 6-ciclopentil-6-[2-(5-ehil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona



Se disolvió 2-{4-[3-ciclopentil-4-(2,2-dimetil-6-oxo-6H-[1,3]dioxin-4-il)-3-hidroxi-but-1-inil]-2-metilfenil}-2-metil-propionitrilo (1,28 g, 3,0 mmol) de la etapa 5 anterior y se trató con $Pd(OH)_2$ (0,38 g, 20% en peso, tipo Degussa). La mezcla se agitó en un globo de hidrógeno durante una noche. La mezcla de reacción se filtró a través de una capa de celite, seguido de lavado con EtOAc. El filtrado se concentró hasta dar un sólido amarillo pálido. El sólido se disolvió en NaOH (0,3 M en MeOH, 15 ml, 4,5 mmol). La reacción se agitó a temperatura ambiente durante 3 horas y después se interrumpió con 75 ml de NH_4Cl saturado y 3 ml de HCl 1 N. A esta solución se le añadieron 100 ml de CH_2Cl_2 y las capas se separaron. La capa acuosa se extrajo con 2 x 75 ml de CH_2Cl_2 y las capas orgánicas se combinaron. Después del secado de la capa orgánica con $MgSO_4$ y del filtrado para retirar los sólidos, el disolvente se retiró por evaporación rotatoria. El aceite restante se purificó por cromatografía ultrarrápida para producir el producto deseado (0,52 g, 47% de rendimiento). ^1H RMN (400 MHz, $CDCl_3$): δ: 1,38-1,40 (1H, m) 1,52 - 1,62 (6 H, m) 1,65 - 1,71 (7 H, m) 1,92 - 1,99 (2 H, m) 2,33 - 2,42 (2 H, m) 2,53 (3 H, s) 2,56 - 2,67 (3 H, m) 5,43 (1H, s) 6,95 - 7,04 (2 H, m) 7,22 (1H, d, J = 8,08 Hz). MS (ESI): 366 (M-H).

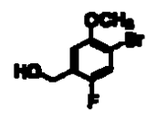
Ejemplo A(79): 2-[4-[2-(2-ciclopentil-4-hidroxi-5-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2il)metil]-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-fluoro-5-hidroxifenil]-2-metilpropanonitrilo



El 2-(4-[2-[1-ciclopentil-3-hidroxi-4-(6-metil-[1,2,4]triazolo[1,5-a]pirimidin-2-

ilmetil)-5-oxociclohex-3-enil]-etil}-2-fluoro-5-metoxi-fenil)-2-metil-propionitrilo de la etapa 2 mostrada a continuación ((168 mg, 0,3 mmol) en CH_2Cl_2 se enfrió a -78°C. Se añadió lentamente tribromuro de boro 1 M (3,06 ml, 3,1 mmol) a -78°C. La mezcla de reacción después se agitó durante 0,5 horas a -78°C y a temperatura ambiente durante 2,5 horas más. A la mezcla de reacción se le añadieron lentamente agua enfriada con hielo (6 ml), seguido HCl concentrado (0,5 ml). La mezcla resultante se agitó durante 0,5 horas más y después se extrajo 3 veces con CH_2Cl_2 (3x75 ml). La capa de CH_2Cl_2 orgánica combinada se lavó con salmuera (75 ml), se secó sobre $MgSO_4$ y se concentró *al vacío*. El residuo se purificó mediante cromatografía en columna ultrarrápida para dar el producto deseado (25 mg, 15% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ: 1,69 - 1,79 (10 H, m) 1,90-1,98 (3 H, m) 2,33-2,43 (2 H, m) 2,45-2,53 (6 H, m) 2,58-2,69 (4 H, m) 4,02-4,16 (2 H, m) 6,78 (1H, d, J = 11,87 Hz) 6,91 (1H, d, J = 6,82 Hz) 8,62 (1H, s) 8,70 (1H, s). MS (ESI): 532 (M-H).

Etapa 1: (4-Bromo-2-fluoro-5-metoxi-fenil)-metanol

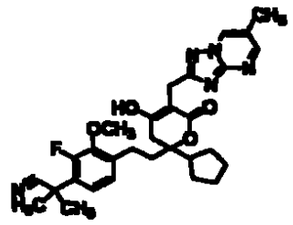


Se añadió lentamente bromo (15 ml, 0,3 mol) a una solución de 2-fluoro-5-metoxibenzaldehído (23,1 g, 0,15 mol) en cloroformo (500 ml) y la mezcla se agitó a temperatura ambiente durante 5 días. La mezcla se vertió en agua (200 ml) y se extrajo con cloroformo (2 x 200 ml). Los extractos orgánicos se lavaron con agua y salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron. El residuo se purificó por cromatografía en columna ultrarrápida (EtOAc al 2-16% en hexanos) para dar 4-bromo-2-fluoro-metoxi-benzaldehído (20,7g, 60%). A una solución de 4-bromo-2-fluoro-5metoxi-benzaldehído (4,0 g, 17,3 mmol) en MeOH a 0°C se le añadió $NaBH_4$ (0,65 g, 17,3 mmol). Después, la mezcla de reacción se agitó a 0°C durante 2 horas y se dejó calentar a temperatura ambiente. La capa orgánica se recogió en éter etílico, se lavó con agua y se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se purificó por cromatografía ultrarrápida (EtOAc al 25-45% en hexanos) para dar el producto. (3,9 g, 99%). ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,90 (s, 3 H), 4,74 (d, J = 6,02 Hz, 2 H), 6,82 (q, J = 6,1Hz, 1H), 7,29 (d, J = 10,58 Hz, 1H).

Etapa 2: 2-(4-{2-[2-ciclopentil-4-hidroxi-5-(6-metil-[1,2,4]triazolo[1,5-a]pirimidin-2-

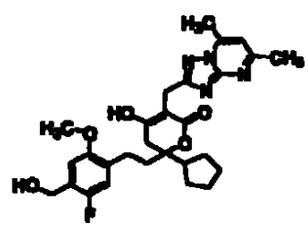
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ilmetil)-6-oxo-3,6-dihidro-2H-piran-2-il]-etil}-2-fluoro-5-metoxi-fenil)-2-metil-propionitrilo



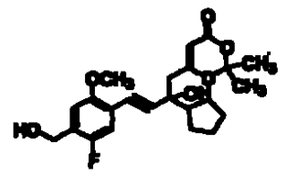
El compuesto del título se preparó de una forma análoga al ejemplo A(78) sustituyendo 4-bromo-2-fluoro-5-metoxi-fenil)-metanol en lugar de (4-bromo-2-metil-fenil)-metanol en la etapa 1 de ese ejemplo. MS (ESI): 546 (M-1)

Ejemplo A(80): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-[5-fluoro-4-(hidroximetil)-2-metoxifenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona



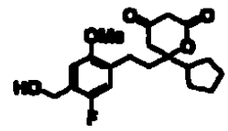
El producto deseado se preparó de una forma análoga al ejemplo A(1) sustituyendo 6-ciclopentil-6-[2-(5-fluoro4-hidroximetil-2-metoxi-fenil)-etil]-dihidro-piran-2,4-diona (364 mg, 1,0 mmol) de la etapa 2 mostrada a continuación en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidropiran-2,4-diona. 52 mg, 12% de rendimiento. ^{1}H RMN (400 MHz, $CDCl_3$) δ:1,53 - 1,57 (2 H, m) 1,92 -2,00 (3 H, m) 2,56-2,75 (12 H, m) 2,79 (3 H, s) 3,78 (3 H, s) 4,12 (2 H, s) 4,68 - 4,72 (3 H, m) 6,76 (1H, d, J = 10,11Hz) 6,81 (1H, d, J = 5,81Hz) 9,93 (1H. s). MS (ESI): 523 (M-H).

Etapa 1: 6-[2-ciclopentil-4-(5-fluoro-4-hidroximetil-2-metoxi-fenil)-2-hidroxi-but-3-inil]-2,2-dimetil-[1,3]dioxin-4-ona



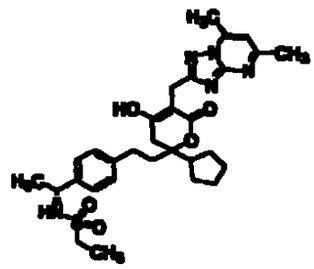
El producto deseado se preparó de una forma análoga a la etapa 5 del ejemplo A(78), sustituyendo (4-bromo-2-fluoro-5-metoxi-fenil)-metanol (2,35 g, 10,0 mmol) de la etapa 1 of A(79) en lugar de 2-(4-bromo-2-metil-fenil)-2-metil-propionitrilo. Rendimiento: 4,4 g, 98%. ^{1}H RMN (400 MHz, $CDCl_3$) δ:11,33 - 1,45 (1H, m) 1,52 - 1,64 (3 H, m) 1,65 - 1,76 (6 H, m) 1,76 - 1,85 (2 H, m) 2,18 - 2,27 (1H, m) 2,37 - 2,49 (1H, m) 2,55 - 2,66 (3 H, m) 3,82 (3 H, s) 4,73 (2 H, s) 5,53 (1H, s) 6,91 - 7,01 (2 H, m). MS (ESI): 417 (M-H).

Etapa 2: 6-ciclopentil-6-[2-(5-fluoro-4-hidroximetil-2-metoxi-fenil)-etil]-dihidro-piran2,4-diona



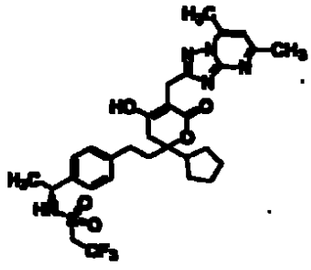
El producto deseado se preparó de una forma análoga al ejemplo A(2), sustituyendo 6-[2-ciclopentil-4-(5-fluoro-4-hidroximetil-2-metoxi-fenil)-2-hidroxi-but-3-inil]-2,2-dimetil-[1,3]dioxin-4-ona (1,28 g, 3,03 mmol) en lugar de 6-[2-ciclopentil-4-(2-etil-5-metoxi-piridin-4-il)-2-hidroxibut-3-inil]-2,2-dimetil-[1,3]dioxin-4-ona. Rendimiento: 1,4 g, 38%. ^{1}H RMN (400 MHz, $CDCl_3$) δ: 1,37 - 1,49 (1H, m) 1,53 - 1,97 (9 H, m) 2,53 - 2,6 (1H, m) 2,64 - 2,7 (1H, m) 2,75 (2 H, s) 3,41 (2 H, s) 3,79 (3 H, s) 4,71 (2 H, s) 6,79 (1H, d, J = 9,85 HZ) 6,87 (1H, d, J = 5,81Hz). MS (ESI): 383 (M-H).

Ejemplo A(81): N-((1R)-1-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)fenil]etil}etanosulfonamida



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo N-((IR)-1-{4-[2-(2ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]fenil)etil)-etanosulfonamida (Ejemplo A(87)en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidropiran-2,4-diona de ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,07 (t, J = 7,3 Hz, 3 H), 1,4(d, J = 6,9 Hz, 3 H), 1,5-1,8 (m, 9 H), 2,11-2,16 (m, 2 H), 2,48-2,59 (m, 7 H), 2,78-2,83 (m, 3 H), 3,71 (d, J = 16 Hz, 1H), 3,85 (d, J = 16 Hz, 1H), 4,03 (t, J = 14, 7,3 Hz, 2 H), 4,39-4,45 (m, 1H), 7,06 (s, 1H), 7,217,31 (m, 4 H), 7,66 (d, J = 8,3 Hz, 1H), 10,9 (s, 1H). Análisis calculado para $C_{30}H_{38}N_6O_6S$: C, 61,94; H, 6,76; N, 12,04, Encontrado: C, 61,80; H, 6,87; N, 12:20, ESIMS (MH+): 582,

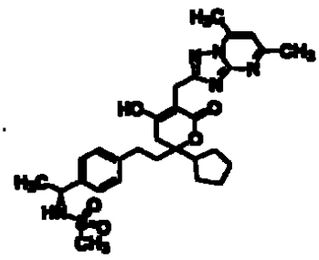
Ejemplo A(82): N-{(1R)-1{4(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)fenil]etil}-2,2,2-trifluoroetanosulfonamida



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo N-((1R)-1-{4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]fenil)etil)-2,2,2-trifluoroetanosulfonamida (Ejemplo A(88)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona de ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,46 (d, J = 6,6 Hz, 3 H), 1,55-1,81 (m, 11H), 2,16-2,20 (m, 2 H), 2,52-2,63 (m, 7 H), 2,81 (d, J = 17 Hz, 1H), 3,77 (d, J = 16 Hz, 1H), 3,9 (d, J = 16 Hz, 1H), 4,22-4,33 (m, 2 H), 4,56-4,63 (m, 1H), 7,09 (s, 1H), 7,27-7,34 (m, 4 H), 8,41 (d, J = 8,3

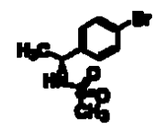
Hz, 1H), 11 (s, 1H). Análisis calculado para $C_{30}H_{38}F_3N_5O_5S$. 0,5 H_2O: C,55,89; H,5,78; N, 10,86. Encontrado: C,56,01; H,5,80; N, 10,94. ESIMS (MH+): 636,

Ejemplo A(83): N-{(1R)-1-[4-(2-(2-ciclopentil-6-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)fenil]etil}metanosulfonamida



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo N-(1-{4-[2-(2-ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]-fenil}-etil)-metanosulfonamida de la etapa 2 mostrada a continuación en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidropiran-2,4-diona de ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,4(d, J = 6,8 Hz, 3 H), 1,5-18,(m, 9 H), 2,10-2,13 (m, 2 H), 2,48-2,64 (m, 10 H), 2,62 (d, J = 17 Hz, 1H), 3,35 (s, 2 H), 3,71-3,88 (m, 2 H), 4,43-4,48 (m, 1H), 7,06 (s, 1H), 7,22-7,31 (m, 4 H), 7,64 (d, J = 8,3 Hz, 1H), 10,88 (s, 1H). Análisis calculado para $C_{28}H_{37}N_5O_6S$: C, 61,36; H, 6,57; N, 12,34, Encontrado: C, 61,47; H, 6,80; N, 12,30.

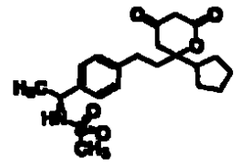
Etapa 1: (R) N-[1-(4-Bromo-fenil)-etil]-metanosulfonamida.



A una solución agitada de (R)-(+)-1-(4-bromofenil)etilamina (0,5 g, 2,49 mmol), en CH_2Cl_2 anhidro (5 ml) en una atmósfera de argón se le añadieron cloruro de metanosulfonilo (0,23 ml, 2,99 mmol) y piridina (0,30 ml, 3,73 mmol). La solución resultante se agitó a 25°C horas. La mezcla de reacción se inactivó con HCl 1 N y se extrajo con EtOAc (30 ml). La fase orgánica se lavó con salmuera (50 ml), se secó sobre Na_2SO_4 y se evaporó. El residuo se purificó por cromatografía en columna ultrarrápida (EtOAc al

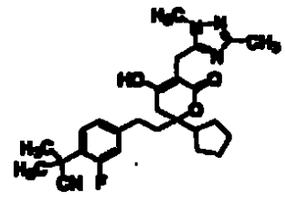
80% en hexanos) para dar el producto (0,40 g,58%) en forma de un sólido blanco. ^{1}H RMN ($CDCl_3$) δ: 1,52 (d, J = 6,8 Hz, 3 H), 2,67 (s, 3 H), 4,61-4,72 (m, 2 H), 7,24 (d, J = 8,3 Hz, 2 H), 7,51 (d, J = 8,3 Hz, 2 H). ESIMS (MNa+): 279,

Etapa 2: N-(1-(4-[2-(2-ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]-fenil}-etil)-metanosulfonamida



El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo N-[1-(4-bromo-fenil)etil]-metanosulfonamida de la etapa 1 anterior en lugar de 4-bromo-2-etil-5-metoxipiridina en la etapa 6 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,52 (d, J = 7,2 Hz, 3 H), 1,58-1,72 (m, 8 H), 1,93-2,05 (m, 2 H), 2,27-2,30 (m, 2 H), 2,66 (s, 3 H), 2,45-2,46 (m, 1H), 2,78 (s, 2 H), 3,42 (d, J = 2,7 Hz, 2 H), 4,54 (d, J = 3,0 Hz, 1H), 4,60-4,65 (m, 1H), 7,15 (d, J = 8,3 Hz, 2 H), 7,26 (d, J = 8,3 Hz, 2 H). Análisis calculado para $C_{21}H_{29}NO_6S$: C, 61,89; H, 7,17, N, 3,44; Encontrado: C, 61,94; H, 7,40, N, 3,59, ESIMS (MH-): 406,

Ejemplo A(84): 2-[4-(2-(2-ciclopentil-5-[(1,3-dimetil-1H-1,2,4-triazol-5-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-fluorofenil]-2-metilpropanonitrilo

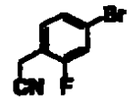


El compuesto del título se preparó de una forma análoga al ejemplo A(1), sustituyendo 2-{4-[2-(2-ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]-2-fluoro-fenil}-2-metil-propionitrilo.de la etapa 3 mostrada a continuación, en lugar de 6-[2-(3-cloro-5-etil-4-metoxi-fenil)-etil]-6-ciclopentil-dihidro-piran2,4-diona y 2,5-dimetil-2H-[1,2,4]triazol-3-carbaldehído en lugar de 5,7dimetil-[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído en ese ejemplo. ^{1}H RMN (300 MHz, $DMSOd_6$): δ 1,49-1,69 (m, 8 H), 1,72 (s, 6 H), 2,06 (s,

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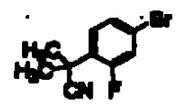
3 H), 2,11 (s, 3 H), 2,12-2,13 (m, 2 H), 2,34-2,42 (m, 1H), 2,55-2,66 (m, 3H), 2,80 (d, J = 17 Hz, 1H), 3,42-3,65 (m, 2 H), 7,08-7,18 (m, 2 H), 7,35-7,40 (m, 1H). Análisis calculado para $C_{27}H_{33}FN_4O_3 \cdot 0,25\ H_2O$: C, 66,85; H, 6,96; N, 11,55, Encontrado: C, 66,88; H, 6,99; N, 11,60. ESIMS (MH+): 481,

Etapa 1: (4-Bromo-2-fluoro-fenil)-acetonitrilo



A una solución de 4-bromo-1-bromometil-2-fluoro-benceno (8,15 g, 30,4 mmol) disuelta en DMF (16 ml) se le añadieron cianuro sódico (2,24 g, 45,6 mmol) y agua (2 ml). La reacción se agitó durante una hora a 70°C. A la reacción se le añadieron 130 ml de agua; 120 ml de $NaHCO_3$ saturado y 100 ml de EtOAc. Las capas se separaron y la capa acuosa se extrajo con 3 x 100 ml de EtOAc. Los extractos orgánicos combinados se lavaron con 100 ml agua y después se secaron sobre Na_2SO_4. Después de retirar por filtración los sólidos, las aguas madre se concentraron hasta obtener el producto deseado por evaporación rotatoria (6,5 g, 99% de rendimiento). MS (APCI): 240 (M+H), 242 (M+2+H).

Etapa 2: 2-(4-Bromo-2-fluoro-fenil)-2-metil-propionitrilo

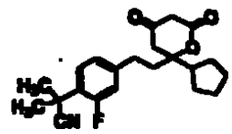


A una suspensión de hidruro sódico (dispersión al 60% en aceite mineral, 0,82 g, 20,6 mmol) en DMF (20 ml) enfriada a 0°C se le añadió una solución de (4-bromo-2-fluoro-fenil)-acetonitrilo (2,0 g, 9,35 mmol) de la etapa 1 anterior, disuelto en THF (10 ml). La reacción se agitó hasta que cesó el desprendimiento de gas y después se añadió lentamente yodometano (1,3 ml, 20,6 mmol). La reacción se agitó durante 30 minutos y después se diluyó con 100 ml de EtOAc. Los sólidos se retiraron por filtración y la capa orgánica se lavó con 100 ml agua. La capa orgánica se secó sobre $MgSO_4$ y después se filtró. Las aguas madre se concentraron por evaporación rotatoria y el producto se destiló a alto vacío (0,3 torr, 45°C). Rendimiento: 2,25 9, 99%. %. ^1H RMN ($CDCl_3$)

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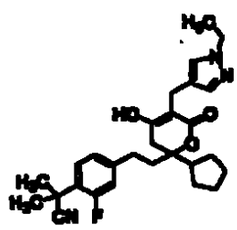
δ: 2,81 (s, 3H), 2,88 (s, 3H), 7,20-7,25 (m, 3H).

Etapa 3: 2-{4-[2-(2-ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]-2-fluoro-fenil}-2-metil-propionitrilo



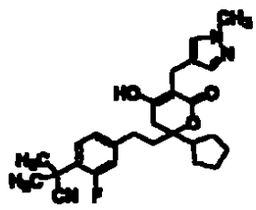
El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo 2-(4-bromo-2-fluoro-fenil)-2-metil-propionitrilo de la etapa 2 anterior en lugar de 4-bromo-2-etil-5-metoxi-piridina en la etapa 6 de ese ejemplo. ^{1}H RMN ($CDCl_3$) δ: 1,60-1,73(m, 6 H), 1,92-1,98 (m, 2 H), 2,22-2,30 (m, 1H), 2,65-2,71 (m, 2 H), 2,75-2,80 (m, 2 H), 6,88-6,96 (m, 2 H), 7,37-7,43 (m, 1H).

Ejemplo A(85): 2-[4(2-(2-ciclopentil-5-[(1-etil-1H-pirazol-4-il)metil-4-hidroxi-6-oxo-3,6dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo



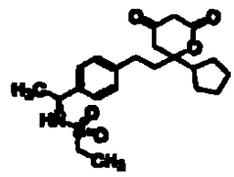
El compuesto del título se preparó de una forma análoga al ejemplo A(84) sustituyendo 1-etil-1H-pirazol-4-carbaldehído en lugar de 2,5-dimetil-2H-[1,2,4]triazol-3-carbaldehído en ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,19 (t, J = 7,4 Hz, 3 H), 1,31-1,52 (m, 8 H), 1,70 (s, 6 H), 1,77-1,98 (m, 2 H), 2,55-2,72 (m, 4H), 3,15-3,19 (m, 2H), 3,84 (m, 2 H), 3,98-4,07 (m, 2 H), 6,66-6,91 (m, 2 H), 7,15-7,34 (m, 3 H). Análisis calculado para $C_{28}H_{34}FN_3O_3 \cdot 0{,}75\ H_2O$: C, 68,20; H, 7,26, N, 8,52, Encontrado: C, 67,87; H, 6,96; N, 8,47. ESIMS (MH+): 480.

Ejemplo A(86): 2-[4(2-(2-ciclopentil-4-hidroxi-5-[(1-metil-1H-pirazol-4-il)metil]-6-oxo-3,6dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo



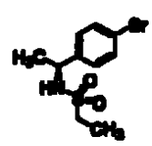
El compuesto del título se preparó de una forma análoga al ejemplo A(84) sustituyendo 1-metil-1H-pirazol4-carbaldehído en lugar de 2,5-dimetil-2H-[1,2,4]triazol-3-carbaldehído en ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,44-1,62 (m, 8 H), 1,72 (s, 6 H), 1,86-1,91 (m, 2 H), 2,302,36 (m, 2 H), 2,54-2,62 (m, 3 H), 2,72 (d, J = 17 Hz, 1H), 3,29-3,30 (m, 2 H), 3,73 (s, 3H), 6,99-7,17 (m, 4 H), 7,33-7,45 (m, 1H)_ Análisis calculado para $C_{27}H_{32}FN_3O_3 \cdot 1{,}0\ H_2O$: C, 67,06; H, 7,09; N, 8,69. Encontrado: C, 67,20; H, 6,76; N, 8,65. ESIMS (MH+): 466,

Ejemplo A(87): N-((1R)-1-{4,{2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]fenil}etil)etanosulfonamida



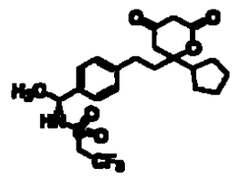
El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo [1-(4-bromo-fenil)-etil]-amida del ácido (R)-etanosulfónico de la etapa 1 mostrada a continuación en lugar de 4-bromo-2-etil-5-metoxi-piridina en la etapa 6 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,22 (t, J = 7,5 Hz, 3 H), 1,53 (d, J = 6,9 Hz, 3 H), 1,54-1,6 (m, 8 H), 1,93-2,05 (m, 2 H), 2,27-2,30 (m, 2 H), 2,46-2,48 (m, 1H), 2,65-2,72 (m, 4 H), 2,77 (s, 2 H), 2,83 (d, J = 17 Hz, 1H), 4,57-4,64 (m, 1H), 7,13-7,15 (m, 2 H), 7,24-7,26 (m, 2 H). ESIMS (MH-): 420.

Etapa 1: [1-(4-bromo-fenil)-etil]-amida del ácido (R)-etanosulfónico



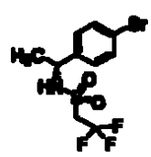
A una solución agitada de (R)-(+)-1-(4-bromofenil)etilamina (1g,5 mmol), en CH_2Cl_2 anhidro (10 ml) en una atmósfera de argón se le añadieron cloruro de etano sulfonilo (0,57 ml,5,99 mmol) y piridina (0,60 ml, 7,5 mmol). La solución resultante se agitó a 25°C durante 3 horas. La mezcla de reacción se inactivó con HCl 1 N y se extrajo con EtOAc (3x10 ml). La fase orgánica se lavó con salmuera (50 ml), se secó sobre Na_2SO_4 y se evaporó. El residuo se purificó por cromatografía en columna ultrarrápida (EtOAc al 80% en hexanos) para dar el producto (0,40 g,58%) en forma de un sólido blanco. ^{1}H RMN ($CDCl_3$) δ: 1,23 (t, J = 7,5 Hz, 3 H), 1,52 (d, J = 6,8 Hz, 3 H), 2,77 (q, J = 14, 7,5 Hz, 2 H), 4,61-4,72 (m, 2 H), 7,24 (d, J = 8,3 Hz, 2 H), 7,51 (d, J = 8,3 Hz, 2 H). ESIMS (MH+): 293.

Ejemplo A(88): N-((1R)-1-(4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]fenil)etil)-2,2,2-trifluoroetanosulfonamida



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo [1-(4-bromo-fenil)-etil]-amida del ácido (R) 2,2,2-trifluoroetanosulfónico de la etapa 1 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxibenceno en la etapa 4 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,17-1,21 (m, 3 H), 1,51-1,6 (m, 8 H), 1,93-2,0 (m, 2 H), 2,27-2,30 (m, 2 H), 2,67-2,70 (m, 2 H), 2,77 (s, 2 H), 3,71-3,74 (m, 2 H), 3,80-3,83 (m, 1H), 4,63-4,72 (m, 1H), 7,16-7,29 (m,5 H). ESIMS (MH-): 474.

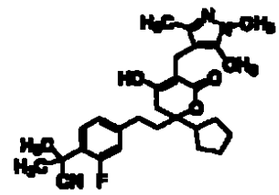
Etapa 1: [1-(4-bromo-fenil)-etil]-amida del ácido (R)-2,2,2-Trifluoro-etanosulfónico



El compuesto del título se preparó de una forma análoga a la etapa 1 del ejem-

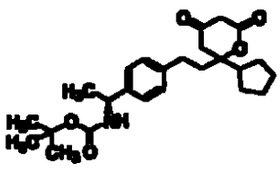
plo A(81) sustituyendo cloruro de 2,2,2trifluoroetanosulfonilo cloruro en lugar de cloruro de etano sulfonilo de ese ejemplo. ^{1}H RMN ($CDCl_3$) δ: 1,53 (d, J = 6,8 Hz, 3 H), 2,70-2,8 (m, 2 H), 4,61-4,72 (m, 2 H), 7,24 (d, J = 8,3 Hz, 2 H), 7,51 (d, J = 8,3 Hz, 2 H). ESIMS (MH+): 345

Ejemplo A(89): 2-[4[2-(2-ciclopentil-4-hidroxi-6-oxo-5-[(1,3,5-trimetil-1H-pirazol-4-il)metil]3,6-dihidro-2H-piran-2-il)etil)-2-fluorofenil]-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo A(84) sustituyendo 1,3,5-trimetil-1Hpirazol-4-carbaldehído en lugar de 2,5-dimetil-2H-[1,2,4]triazol-3-carbaldehído en ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,45-1,69 (m, 8 H), 1,72 (s, 6 H), 1,82-1,88 (m, 2 H), 2,03 (s, 3 H), 2,12 (s, 3 H), 2,26-2,31 (m, 1H), 2,49-2,58 (m, 3 H), 2,71 (d, J = 17 Hz, 1H), 3,12 (d, J = 14 Hz, 1H), 3,24 (d, J = 14 Hz, 1H), 3,54 (s, 3 H), 6,94 (dd, J =8,4, 1,8 Hz, 1H), 7,04 (dd, J = 13, 1,8 Hz, 1H), 7,36 (t, J =8,4 Hz 1H), 10,68 (s, 1H). Análisis calculado para $C_{29}H_{36}FN_3O_3$: C, 70,56; H, 7,35; N, 8,51, Encontrado: C, 70,70; H, 7,45; N, 8,50. ESIMS (MH+): 494.

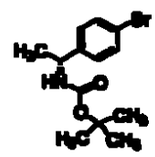
Ejemplo A(90): (1R)-1-(4[2-2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]fenil)etilcarbamato de terc-butilo



El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo *éster terc*-butílico del ácido (R)-(1-(4-bromofenil)-etil]-carbámico de la etapa 1 mostrada a continuación en lugar de 4-bromo-2etil-5-metoxi-piridina en la etapa 6 de ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6): - 1,18 (d, J = 6,6 Hz, 3 H), 1,35-1,69 (m, 17 H), 1,94-1,98 (m, 2H), 2,27-2,31 (m, 1H), 2,63-2,69 (m, 2 H), 2,77 (s, 2 H), 3,42 (s, 2

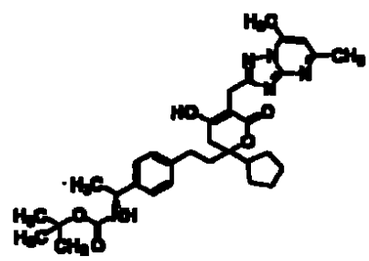
H), 3,81-3,88 (m, 1H), 4,76 (s a, 1H), 7,10 (d, J = 8,1Hz, 2 H), 7,23 (d, J = 8,1Hz, 2 H). ESIMS (MH+): 430.

Etapa 1: éster terc-butílico del ácido (R)-(1-(4-bromofenil)-etil]-carbámico



A una solución agitada de (R)-(+)-1-(4-bromofenil)etilamina (5 g, 24,99 mmol), en dioxano (50 ml) en una atmósfera de argón se añadieron dicarbonato de di-terc-butilo (6 g, 27,5 mmol) y NaOH 0,5 M (50 ml). La solución resultante se agitó a 25°C una noche. La mezcla de reacción se repartió entre acetato de etilo y ácido cítrico al 10% y se extrajo con acetato de etilo (3x100 ml). La fase orgánica se lavó con salmuera (50 ml), se secó sobre Na_2SO_4 y se evaporó. El residuo se solidificó hasta dar un sólido blanco y se usó sin purificación adicional. (7 g, 93%). ^{1}H RMN ($CDCl_3$) δ: 1,32-1,34 (m, 12 H), 4,68-4,71 (m, 2 H), 7,29-7,12 (m, 2H), 7,36-7,39 (m, 2H). ESIMS (MH+): 302.

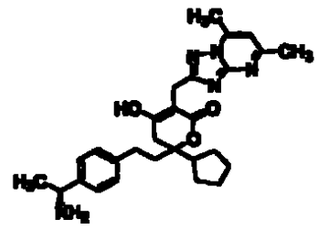
Ejemplo A(91): (1R)-1-[4-(2{2-ciclopentil-5-[(5,7-dimetil[1,2,4]-triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)fenil]etilcarbamato de terc-butilo



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo (1R)-1{4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]fenil}-etilcarbamato de terc-butilo (Ejemplo A(90) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona de ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,24-1,66 (m, 21H), 2,06-2,08 (m, 2H), 2,42-2,61 (m, 9 H), 2,77 (d, J = 16

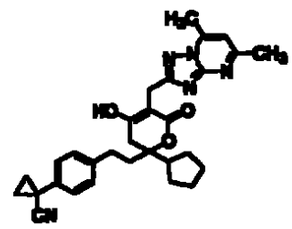
Hz, 1H), 3,73 (d, J = 16 Hz, 1H), 3,82 (d, J = 16 Hz, 1H), 4,33-4,55 (m, 1H), 7,05-7,08 (m, 1H), 7,29-7,40 (m, 4 H), 8,35 (s, 1H), 11 (s, 1H). ESIMS (MH+): 590.

Ejemplo A(92): 6-(2-(4-[(1R)-1-Aminoetil]fenil}etil)-6-ciclopentil3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



A una solución agitada de (1R)-1-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5a]pirimidin-2-il)metil]-4-hidroxi-oxo-3,6-dihidro-2H-piran-2-il}etil)fenil]etilcarbamato de terc-butilo (0,58g, 0,98 mmol, ejemplo A(91)) en dioxano (2 ml) en una atmósfera de argón se le añadió HCl 4 N en dioxano (2 ml). La solución resultante se agitó a 25°C durante 30 minutos. Los disolventes se evaporaron completamente y el sólido blanco resultante se recristalizó en acetato de etilo para dar el producto (0,40 g, 80%) en forma de un sólido blanco. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,56-1,77 (m, 11H), 2,14-2,18 (m, 2H), 2,57-2,86 (m, 10 H), 3,77-3,94 (m, 2 H), 4,40-4,43 (m, 1H), 6,6 (s a, 2 H), 7,21 (s, 1H), 7,38 (d, J = 7,9 Hz, 2 H), 7,48 (d, J = 7,9 Hz, 2 H), 8,56 (s, 1H), 11,2 (s, 1H). Análisis calculado para $C_{28}H_{38}N_6O_3$. 1,0 HCl 1,0 H20: C, 63,74; H, 7,26; N, 13,27, Encontrado: C, 63,60; H, 7,48; N, 13,20. ESIMS (MH+): 527.

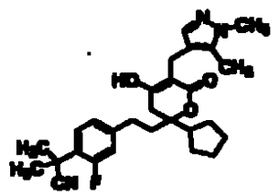
Ejemplo A(93): 1-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-4-oxo-3,6,dihidro-2H-piran-2-il)etil)fenil]ciclopropanocarbonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo A(1) susti-

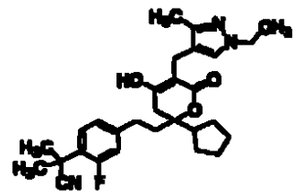
tuyendo 1-(4bromofenil)ciclopropanocarbonitrilo en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6): δ 1,44 - 1,48 (m, 2 H), 1,5-1,7 (m, 8H), 1,73-1,77 (m, 2 H), 2,10-2,15 (m, 2H), 2,50-2,60 (m,11H), 2,82(d, J = 16 Hz, 1H), 3,73 (d, J = 16 Hz, 1H), 3,85 (d, J = 16 Hz, 1H), 7,08 (s, 1H), 7,23-7,32 (m, 4H), 10,87 (s, 1H). ESIMS (MH+): 512.

Ejemplo A(94): 2-[4(2-(2-ciclopentil-5-[(1,5-dimetil-1H-pirazol-4-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-fluorofenil]-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo A(84) sustituyendo 1,5-dimetil-1H-pirazol-4-carbaldehído en lugar de 2,5-dimetil-2H-[1,2,4]triazol-3-carbaldehído en ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,47-1,66 (m, 8 H), 1,72 (s, 6 H), 1,82-1,89 (m, 2 H), 2,11 (s, 3 H), 2,18 (s, 3 H), 2,29-2,32 (m, 1H), 2,49-2,56 (m, 3 H), 2,70 (d, J = 16 Hz, 1H), 3,16-3,28 (m, 2 H), 6,96-7,09 (m, 3 H). 7,33-7,39 (m, 1H), 10,7 (s, 1H). Análisis calculado para $C_{28}H_{34}FN_3O_3$. 0,5 H_2O: C, 68,83; H, 7,22; N, 8,60. Encontrado: C, 68,96; H, 7,23; N, 8,60. ESIMS (MH+): 480

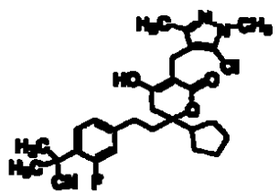
Ejemplo A(95): 2-[4-(2-(2-ciclopentil-5-[(1-etil-3-metil-1H-pirazol-4-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo A(84) sustituyendo 1-etil-3-metil-1H-pirazol-4-carbaldehído en lugar de 2,5-dimetil-2H-[1,2,4]triazol-3-carbaldehído en ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,22 (t, J = 7,2 Hz, 3 H), 1,45-1,67 (m, 8 H), 1,72 (s, 6 H), 1,88-1,93 (m, 2H), 2,10 (s, 3 H), 2,19-2,31 (m, 1H), 2,53-2,61 (m, 2 H), 2,72 (d, J = 16 Hz, 1H), 3,17 (d, J = 17 Hz, 1H), 3,25

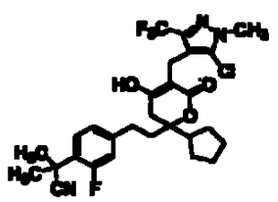
(d, J = 17 Hz, 1H), 3,90 (q, J = 14, 7,2 Hz, 2 H), 6,98-7,01 (m, 1H), 7,00 (dd, J = 8, 1,6 Hz, 1H), 7,10 (cid, J = 13, 1,6 Hz, 1H), 7,16 (s, 1H), 7,36 (t, J = 8 Hz, 1H), 10,8 (s, 1H). Análisis calculado para $C_{48}H_{38}FN_3O_3$, 0,5 H_2O: C, 69,30; H, 7,42; N, 8,36, Encontrado: C, 69,38; H, 7,43; N, 8,39. ESIMS (MH+): 494.

Ejemplo A(96): 2-[4-(2-{5-[(5-cloro-1,3-dimetil-1H-pirazol-4-il)metil]-2-ciclopentil-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo A(84) sustituyendo 5-cloro-1,3-dimetil1H-pirazol-4-carbaldehído en lugar de 2,5-dimetil-2H-[1,2,4]triazol-3-carbaldehído en ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,42-1,67 (m, 8 H), 1,73 (s, 6 H), 1,88-1,93 (m, 2 H), 2,08 (s, 3 H), 2,11 (s, 3 H), 2,28-2,31 (m, 1H), 2,51-2,61 (m, 3 H), 2,70 (d, J = 17 Hz, 1H), 3,20 (d, J = 14 Hz, 1H), 3,28 (d, J = 14 Hz, 1H), 7,00 (cid, J = 8,2, 1,7 Hz, 1H), 7,08 (dd, J = 13, 1,7 Hz, 1H), 7,36 (t, J = 8,2 Hz 1H), 10,8 (s, 1H). Análisis calculado para $C_{28}H_{33}FClN_3O_3$. 0,25 H_2O: C, 64,86; H, 6,51; N, 8,10. Encontrado: C, 64,73; H, 6,42; N, 8,08. ESIMS (MH+): 515.

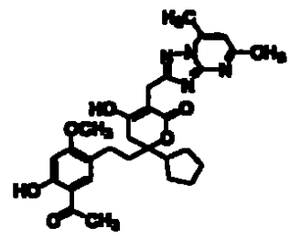
Ejemplo A(97): 2-(4-[2-(5-[[5-cloro-1-metil-3-(trifluorometil)-1H-pirazol-4-il]metil}-2-ciclopentil-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil]-2-fluorofenil}-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo A(84) sustituyendo 5-cloro-1-metil-3-trifluorometil-1H-pirazol-4-carbaldehído en lugar de 2,5-dimetil-2H[1,2,4]triazol-3-carbaldehído en ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6):

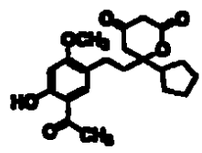
δ 1,48-1,67 (m, 8 H), 1,76 (s, 6 H), 1,95-1,98 (m, 2 H), 2,38-2,40 (s, 1H), 2,56-2,72 (m, 4 H), 3,39-3,48 (m, 2 H), 3,86 (s, 3 H), 7,06-7,16 (m, 2 H), 7,37-7,43 (m, 1H), 11 (s, 1H). Análisis calculado para $C_{29}H_{30}F_4ClN_3O_3$: C,59,21; H,5,32; N, 7,40, Encontrado: C,59,04; H,5,31; N, 7,32. ESIMS (MH+): 569.

Ejemplo A(98): 6-[2-(5-Acetil-4-hidroxi-2-metoxifenil)etil]-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 6-[2-(5-acetil-4-hidroxi-2-metoxifenil)etil]-6-ciclopentildihidro-2H-piran-2,4(3H)-diona (Ejemplo A(99) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona de ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,34-1,66 (m, 8 H), 1,8-2,06 (m, 3 H), 2,32-2,49 (m, 12 H), 2,65 (d, J = 17 Hz, 1H), 3,57-3,72 (m, 6 H), 6,31 (s, 1H), 6,90 (s, 1H), 7,46 (s, 1H), 12,52 (s, 1H). Análisis calculado para $C_{29}H_{34}N_4O_6$. 0,25 $H_2$0: C, 64,61; H, 6,45; N, 10,39, Encontrado: C, 64,57; H, 6,39; N, 10,22. ESIMS (MH+): 535.

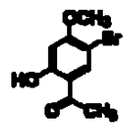
Ejemplo A(99): 6-[2-(5-Acetil-4-hidroxi-2-metoxifenil)etil]-6-ciclopentil-dihidro-2H-piran-2,4(3H)-diona



El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo 1-(5-bromo-2-hidroxi4-metoxi-fenil)-etanona de la etapa 1 mostrada a continuación en lugar de 4-bromo-2-etil-5-metoxi-piridina en la etapa 6 de ese ejemplo. ^{1}H

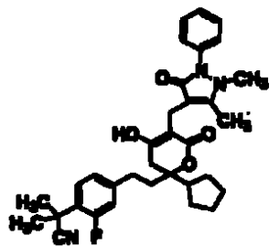
RMN (300 MHz, $CDCl_3$): δ 1,51-1,54 (m, 8H), 1,80-1,95 (m, 2H), 2,29-2,36 (m, 1H), 2,57 (s, 3H), 2,57-2,67 (m, 2H), 2,75 (s, 2H), 3,41 (s, 2H), 3,74 (s, 3H), 6,45 (s, 1H), 7,87 (s, 1H), 12,60 (s, 1H). ESIMS (MH-): 374.

Etapa 1: 1-(5-Bromo-2-hidroxi-4-metoxi-fenil)-etanona.



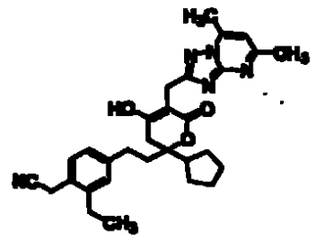
El compuesto del título se preparó de una forma análoga a la etapa 3 del ejemplo A(22) sustituyendo 2'-hidroxi-4'-metoxiacetofenona en lugar de 5-etoxi-2-etil-fenol de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,56 (s, 3H), 3,93 (s, 3H), 6,46 (s, 1H), 7,87 (s, 1H), 12,67 (s, 1H). ESIMS (MH-): 244.

Ejemplo A(100): 2-[4-(2-(2-ciclopentil-5-[(1,5-dimetil-3-oxo-2-fenil-2,3-dihidro-1H-pirazol-4il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-fluorofenil]-2-metilpropanonitrilo



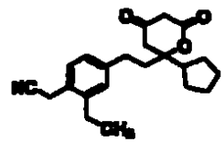
El compuesto del título se preparó de una forma análoga al ejemplo A(84) sustituyendo 1,5-dimetil-3-oxo-2-fenil-2,3-dihidro-1H-pirazol-4-carbaldehído en lugar de 2,5-dimetil-2H[1,2,4]triazol-3-carbaldehído en ese ejemplo. °H RMN (300 MHz, DMSO-d_6): δ 1,45-1,67 (m, 8 H), 1,71 (s, 6 H), 1,88-1,94 (m, 2 H), 2,27-2,30 (m, 1H), 2,37 (s, 3 H), 2,53-2,65 (m, 4 H), 3,12 (s, 3 H), 3,13-3,18 (m, 2 H), 7,05-7,17 (m,2 H), 7,34-7,41 (m,5 H), 7,51-7,56 (m, 1H), 12,3 (s, 1H). ESIMS (MH+): 572.

Ejemplo A(101): [4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-etilfenil]acetonitrilo



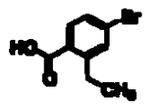
A una solución de {4[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-etilfenil}acetonitrilo (200 mg, 0,57 mmol, ejemplo A(102)) en MeOH anhidro (6 ml) a temperatura ambiente se le añadió 5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído (120 mg, 0,68 mmol). La mezcla se agitó durante 5 min antes de añadir complejo de borano-dimetilamina (37 mg, 0,62 mmol). La reacción se agitó a esta temperatura durante 15 horas antes de interrumpirse por la adición de HCl 1,0 N. El disolvente se retiró y el residuo se purificó por HPLC para obtener el producto deseado (60 mg, 21% de rendimiento). ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,03 (t, J = 7,5 Hz, 3 H), 1,32-1,64 (m, 8 H), 2,06 (m, 2 H), 2,36-2,55 (m, 12 H), 2,73 (d, J = 17,9 Hz, 1H), 3,64 (d, J = 16,1Hz, 1H), 3,77 (d, J = 16,4 Hz, 1H), 3,89 (s, 2 H), 6,95 (s, 1H), 7,00 (s, 1H), 7,04 (d, J = 7,7 Hz, 1H), 7,17 (d, J = 7,7 Hz, 1H), 10,81 (s, 1H).

Ejemplo A(102): (4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-etilfenil}acetonitrilo



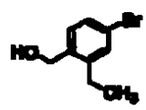
El compuesto del título se preparó de una forma análoga al ejemplo A(2), sustituyendo (4-bromo-2-etilfenil)-acetonitrilo (etapa 4 mostrada a continuación) en lugar de 4-bromo-2-etil-5-metoxi-piridina (etapa 6). ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,25 (t, J = 7,5 Hz, 3 H), 1,41-1,83 (m, 8H), 1,97 (m, 2 H), 2,27 (m, 1H), 2,65 (m, 4 H), 2,78 (s, 2 H), 3,43 (s, 2 H), 3,67 (s, 2 H), 7,01 (m, 2 H), 7,29 (d, J = 8,3 Hz, 1H).

Etapa 1: Ácido 4-bromo-2-etil-benzoico (4641-144)



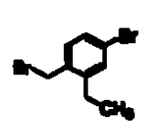
El compuesto del título e preparó de acuerdo con el procedimiento bibliográfico citado a continuación. *J. Med. Chem.*, 1997, 40, 2017-2034,

Etapa 2: (4-Bromo-2-etil-fenil)-metanol



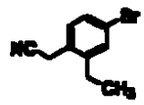
A una solución de ácido 4-bromo-2-etil-benzoico (115 mmol) en THF anhidro (380 ml) a 0°C se le añadió complejo de BH_3-THF (solución 1,0 N en THF, 230 ml) durante 30 min. La mezcla resultante se calentó lentamente a temperatura ambiente y se agitó durante 15 horas. La reacción se interrumpió cuidadosamente con la adición lenta de agua. El disolvente se retiró y el residuo se recogió en EtOAc. La capa orgánica se lavó con HCl 1,0 N, H_2O y salmuera y se secó sobre $MgSO_4$. El disolvente se retiró para producir el producto deseado. (22g, rendimiento de 89%) ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,23 (t, J = 7,5 Hz, 3 H), 2,64-3,01 (m, 2H), 4,68 (s, 2H), 7,24-7,26 (m, 1H), 7,32-7,36 (m, 2H).

Etapa 3: 4-Bromo-1-bromometil-2-etil-benceno



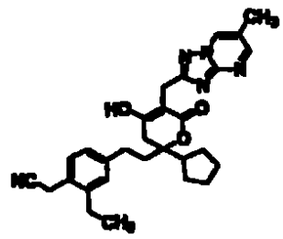
A una solución de (4-bromo-2-etil-fenil)-metanol (7,9 g, 36,7 mmol) en $CHCl_3$ anhidro (122 ml) se le añadió PBr_3 (4,2 ml, 44,1 mmol). La mezcla resultante se agitó a temperatura ambiente durante 2 horas antes de inactivarse por la adición de agua. La capa orgánica se lavó con $NaHCO_3$ y salmuera y se secó sobre $MgSO_4$. El disolvente se retiró al vacío *y* el residuo se filtró a través de una capa de gel de sílice con EtOAc al 20% en hexanos. El disolvente se retiró en *vacuo* para producir el producto deseado (8,4 g, 83%). ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,29 (t, J = 7,5 Hz, 3 H), 2,712,78 (m, 2 H), 4,48 (s, 2H), 7,17-7,20 (m, 1H), 7,28-7,32 (m, 1H), 7,36-7,38 (m, 1H).

Etapa 4: (4-Bromo-2-etil-fenil)-acetonitrilo



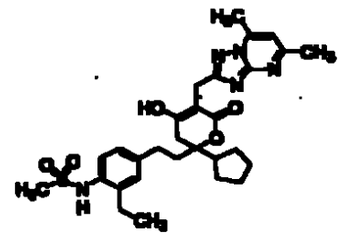
A una solución de 4-bromo-1-bromometil-2-etil-benceno (2,0 g, 7,25 mmol) en DMF/H_2O (30 ml/6 ml) se le añadió cianuro potásico (471 mg, 7,25 mmol). La mezcla de reacción se calentó a 45°C durante 3 horas antes de enfriarse a temperatura ambiente. La mezcla se diluyó con Et_2O y se lavó con H_2O y salmuera y se secó sobre $MgSO_4$. El disolvente se retiró al vacío para obtener el producto deseado (1,33g, 80% de rendimiento). ^1H RMN (300 MHz, $CDCl_3$): δ 1,26 (t, J = 7,5 Hz, 3 H), 2,60-2,67 (m, 2 H), 3,66 (s, 2H), 7,23-7,26 (m, 1H), 7,35-7,36 (m, 1H), 7,38-7,40 (m, 1H).

Ejemplo A(103): [4-(2-(2-ciclopentil-4-hidroxi-6-[(6-metil[1,2,4]triazolo[1,5-a)pirimidin-2-il)metil]-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-etilfenil]acetonitrilo



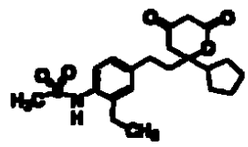
El compuesto del título se preparó de una forma análoga al ejemplo A(101), sustituyendo 6metil[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído en lugar de 5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído. ^1H RMN (300 MHz, DMSO-d_6): δ 1,15 (t, J = 7,5 Hz, 3 H), 1,38-1,71 (m, 8 H), 2,11 (m, 2 H), 2,38 (s, 3 H), 2,42-2,66 (m, 6 H), 2,82 (d, J = 18,2 Hz, 1H), 3,76 (d, J = 16,2 Hz, 1H), 3,84 (d, J = 16,1Hz, 1H), 3,98 (s, 2 H), 7,11 (m, 2 H), 7,27 (d, J = 8,3 Hz, 1H), 8,71 (s, 1H), 8,96 (s, 1H), 10,88 (s, 1H).

Ejemplo A(104): N-[4-(2[2-ciclopentil-6-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il]etil)-2-etilfenil]metanosulfonamida



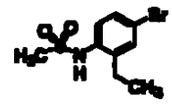
El compuesto del título se preparó de una forma análoga al ejemplo A(101) sustituyendo N-(4-[2-(2-ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]-2-etil-fenil)-metanosulfonamida en lugar de {4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-etilfenil}acetonitrilo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,11 (t, J = 7,5 Hz, 3 H), 1,41-174 (m, 8 H), 2,13 (m, 2 H), 2,47 (s, 3 H), 2,51-2,70 (m, 9 H), 2,83 (d, J = 17,7 Hz, 1H), 2,98 (s, 3 H), 3,74 (d, J = 16,4 Hz, 1H), 3,85 (d, J = 16,2 Hz, 1H), 7,04 (s, 1H), 7,11 (m, 2 H), 7,20 (d, J = 8,6 Hz, 1H), 8,94 (s, 1H), 10,86 (s, 1H).

Ejemplo A(105): N{4[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-etilfenil}metanosulfonamida



El compuesto del título se preparó de una forma análoga al ejemplo A(2), sustituyendo N-(4-bromo-2-etilfenil)-metanosulfonamida en lugar de 4-bromo-2-etil-5-metoxipiridina (etapa 6). ^{1}H RMN (300 MHz, DMSO): δ 1,07 (t, J = 7,5 Hz, 3 H), 1,46-1,70 (m, 8H), 1,89-1,95 (m, 2 H), 2,27-2,38 (m, 1H), 2,56-2,73 (m, 4 H), 2,96 (s, 3 H), 3,42-3,49 (m, 4 H), 4,99 (s, 1H), 7,00-7,03 (m, 1H), 7,09-7,11 (m, 1H), 7,17-7,19 (m, 1H). MS (ESI) (M+Na$^+$): calculado para $C_{21}H_{28}NO_5S$: 430, encontrado 430,

Etapa 1: N-(4-Bromo-2-etil-fenil)-metanosulfonamida

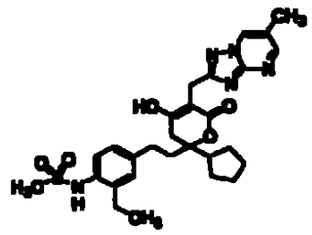


Se trató 4-bromo-2-etil-anilina (2 ml, 14 mmol) disuelta en piridina anhidra (35

SAG 548

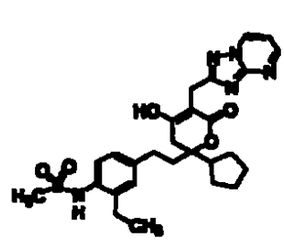
ml) a temperatura ambiente con cloruro de metanosulfonilo (1,3 ml, 16,8 mmol). La reacción se agitó a esta temperatura durante 15 horas antes de diluirse con EtOAc. La mezcla se lavó con H_2O y salmuera y se secó sobre $MgSO_4$. El disolvente se retiró al vacío y el residuo se purificó por cromatografía ultrarrápida (SiO2, EtOAc al 5-30% en hexanos) para producir el producto deseado (3,1 g, 81 de rendimiento). ^1H RMN (300 MHz, $CDCl_3$): δ 1,25 (t, J = 7,5 Hz, 3 H), 2,61-2,68 (m, 2 H), 3,02 (s, 3 H), 6,36 (s, 1H), 7,36-7,39 (m, 3 H).

Ejemplo A(106): N-[4-(2-{2-ciclopentil-4-hidroxi-5-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2il)metil]-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilfenil]metanosulfonamida



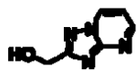
El compuesto del título se preparó de una forma análoga al ejemplo A(104), sustituyendo 6metil[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído en lugar de 5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído. ^1H RMN (300 MHz, DMSO-d_6): δ 0,93 (t, J = 7,3 Hz, 3 H), 1,19-1,54 (m, 8 H), 1,88 (m, 2 H), 2,18 9s, 3 H), 2,28-2,55 (m, 6 H), 2,62 (d, J = 17,0 Hz, 1H), 2,79 (s, 3 H), 3,56 (d, J-15,8 Hz, 1H), 3,65 (d, J = 16,1Hz, 1H), 6,90 (d, J = 7,54 Hz, 1H), 6,93 (s, 1H), 7,01 (d, J = 7,9 Hz, 1H), 8,51 (d, J = 2,4 Hz, 1H), 8,75 (s, 1H), 6,79 (s, 1H), 10,69 (s, 1H).

Ejemplo A(107): N-(4-(2-[2-ciclopentil-4-hidroxi-6-oxo-5-([1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil)-3,6-dihidro-2H-piran-2-il]etil)-2-etilfenil)metanosulfonamida



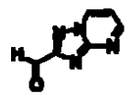
El compuesto del título se preparó de una forma análoga al ejemplo A(104) sustituyendo [1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído de la etapa 2 mostrada a continuación en lugar de 5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,08 (t, J = 7,2 Hz, 3 H), 1,27-1,71 (m, 8 H), 2,11 (m 2 H), 2,48-2,75 (m, 6 H), 2,83 (d, J = 17,1Hz, 1H), 2,99 (s, 3 H), 3,78 (d, J = 15,8 Hz, 1H), 3,87 (d, J = 16,2 Hz, 1H), 7,08 (d, J = 6,2 Hz, 1H), 7,13 (s, 1H), 7,21 (d, J = 8,3 Hz, 1H), 7,27 (dd, J = 6,6, 4,3 Hz, 1H), 8,81 (d, J = 4,3, 1,9 Hz, 1H), 8,95 (s, 1H), 9,07 (dd, J = 6,6, 1,9 Hz, 1H), 10,9 (s, 1H).

Etapa 1: [1,2,4]Triazolo[1,5-a]pirimidin-2-ilmetanol



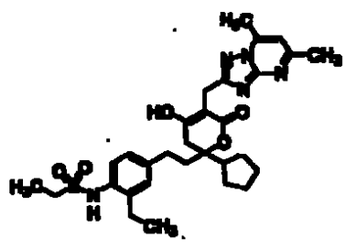
El compuesto del título se preparó de una forma análoga a la etapa 7 del ejemplo A(1) sustituyendo malonaldehído bis(dimetilacetal) en lugar de 2,4-pentanodiona.

Etapa 2: [1,2,4]Triazolo[1,5-a]pirimidina-2-carbaldehído



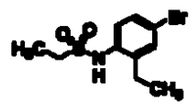
El compuesto del título se preparó de una forma análoga a la etapa 8 del ejemplo A(1) sustituyendo [1,2,4]triazolo[1,5-a]pirimidin-2-ilmetanol en lugar de 5,7-dimetil-[1,2,4]triazolo[1,5-a]pirimidin-2-il)-metanol.

Ejemplo A(108): N-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilfenil]etanosulfonamida



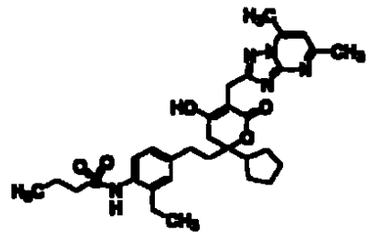
El compuesto del título se preparó de una forma análoga al ejemplo A(104) sustituyendo (4-bromo-2-etil-fenil)-amida del ácido etanosulfónico en lugar de (4-bromo-2-etil-fenil)-amida del ácido metanosulfónico. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,02 (t, J = 7,5 Hz, 3 H), 1,05 (t, J = 7,5 Hz, 3 H), 1,29-1,67 (m, 9H), 2,02-2,09 (m, 2 H), 2,38 (s, 3 H), 2,48 (s, 3 H), 2,51-2,56 (m, 2 H), 2,57-2,64 (m, 2 H), 2,71-2,77 (m, 1H), 2,95-3,02 (m, 2 H), 3,62-3,80 (m, 4 H), 6,95-6,96 (m, 1H), 7,00-7,04 (m, 2 H), 7,06-7,09 (m, 1H).

Etapa 1: (4-bromo-2-etil-fenil)-amida del ácido etanosulfónico



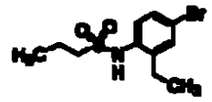
El compuesto del título se preparó de una forma análoga a la etapa 1 del ejemplo A(105), sustituyendo cloruro de etilsulfonilo en lugar de cloruro de metilsulfonilo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,26 (t, J = 8,0 Hz, 3 H), 1,39 (t, J = 8,0 Hz, 3 H), 2,60-2,66 (m, 2 H), 3,12-3,18 (m, 2 H), 7,32-7,37 (m, 3 H).

Ejemplo A(109): N-(4-(2-{2-ciclopentil-5-((5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilfenil]propano-1-sulfonamida



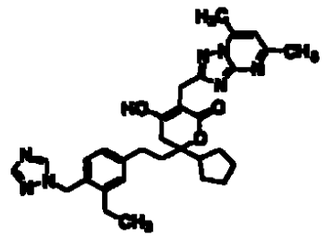
El compuesto del título se preparó de una forma análoga al ejemplo A(104), sustituyendo (4-bromo-2-etil-fenil)-amida del ácido propanosulfónico en lugar de (4-bromo-2-etil-fenil)-amida del ácido metanosulfónico. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,00 (t, J = 7,5 Hz, 3 H), 1,11 (t, J = 7,5 Hz, 3 H), 1,55-1,81 (m, 11H), 2,11-2,17 (m, 2 H), 2,47 (s, 3 H), 2,57 (s, 3 H), 2,62-2,72 (m, 6 H), 3,02-3,07 (m, 2 H), 3,71-3,88 (m, 2 H), 7,04 (s, 1H), 7,10-7,18 (m, 3 H).

Etapa 1: (4-bromo-2-etil-fenil)-amida del ácido propano-1-sulfónico



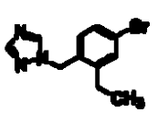
El compuesto del título se preparó de una forma análoga a la etapa 1 del ejemplo A(105), sustituyendo cloruro de propano1-sulfonilo en lugar de cloruro de metilsulfonilo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,04 (t, J = 8,0 Hz, 3 H), 1,25 (t, J = 8,0 Hz, 3 H), 1,81-1,91 (m, 2 H), 2,60-2,66 (m, 2 H), 3,07-3,10 (m, 2 H), 6,29 (s, 1H), 7,32-7,37 (m, 3 H).

Ejemplo A(110): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-[3etil-4-(1H-1,2,4-triazol-1-ilmetil)feniletil}-4hidroxi-5,6-dihidro-2H-piran-2-ona



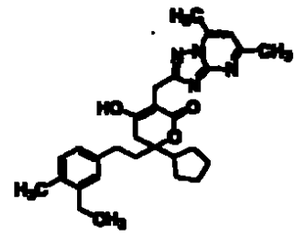
El compuesto del título se preparó de una forma análoga al ejemplo A(101) sustituyendo 1-(4-bromo-2-etilbencil)-1H-[l,2,4]triazol en lugar de {4-[2-(2-ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]-2-etil-fenil}-acetonitrilo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 0,95 (t, J = 7,5 Hz, 3 H), 1,31-1,62 (m, 8 H), 2,03 (m 2 H), 2,31 (s, 3 H), 2,35-2,62 (m, 9 H), 2,74 (d, J = 19,8 Hz, 1H), 3,64 (d, J = 16,6 Hz, 1H), 3,76 (d, J = 17,5 Hz, 1H),5,33 (s, 2 H), 6,92 (d, J = 8,5 Hz, 1H), 6,94 (s, 1H), 6,98 (s, 1H), 6,99 (d, J = 9,2 Hz, 1H), 7,93 (s, 1H), 8,54 (s, 1H), 10,77 (s, 1H).

Etapa 1: 1-(4-Brorno-2-etil-bencil)-1H-[1,2,4]triazol



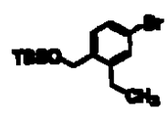
Se trató triazol (275 mg, 3,99 mmol) disuelto en DMF anhidra (15 ml) con NaH (60%, 153 mg). Después de 5 minutos, se añadió 4-bromo-1-bromometil-2-etil-benceno. La mezcla de reacción se calentó a 75°C durante 5 horas antes de enfriarse a temperatura ambiente. La mezcla se diluyó con Et_2O y se lavó con H_2O y salmuera y se secó sobre $MgSO_4$. El disolvente se retiró al vacío para producir el producto deseado (580 mg,55% de rendimiento). ^1H RMN (300 MHz, $CDCl_3$): δ 1,10 (t, J = 7,5 Hz, 3 H), 2,68-2,73 (m, 2 H),5,46 (s, 2 H), 7,01-7,04 (m, 1H), 7,38-7,48 (m, 2 H), 7,97-8,01 (m, 2 H).

Ejemplo A(111): 6,ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil-6-[2-(3-etil-4-metilfenil)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



A una solución de 6-[2-ciclopentil-4-(3-etil-4-metil-fenil)-2-hidroxi-butil]-2,2-dimetil-[1,3]dioxin-4-ona (1,0 g, 1,94 mmol) se le añadió K_2CO_3 (1,07 g, 7,75 mmol). La mezcla se calentó a 45°C durante 45 minutos antes de enfriarse a temperatura ambiente. La reacción se diluyó con H_2O y se lavó con éter isopropílico. La capa acuosa se acidificó a pH 1 con HCl 1,0 N y se extrajo con EtOAc. La capa orgánica se lavó con H_2O y salmuera, se secó sobre $MgSO_4$ y se concentró a presión reducida para producir el producto deseado. (0,63g, rendimiento de 71%) ^1H RMN (300 MHz, DMSO-d_6): δ 0,98(t, J = 7,5 Hz, 3 H), 1,32-1,64 (m, 8 H), 2,04 (m, 2 H), 2,12 (s, 3 H), 2,33-2,51 (m, 12 H), 2,71 (d, J = 17,5 Hz, 1H), 3,64 (d, J = 16,0 Hz, 1H), 3,74 (d, J-16,2 Hz, 1H), 6,83 (d, J = 7,7 Hz, 1H), 6,84 (s, 1H), 6,92 (d, J = 7,3 Hz, 1H), 6,96 (s, 1H), 10,75 (s, 1H).

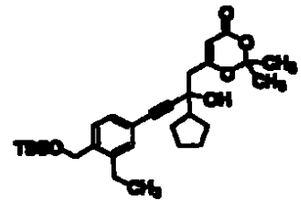
Etapa 1: (4-Bromo-2-etil-benciloxi)-terc-butil-dimetil-silano



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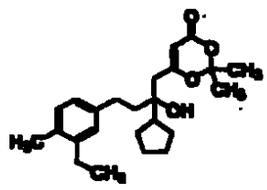
A una solución de (4-bromo-2-etil-fenil)-metanol en DMF anhidra se le añadió TBSCl (1,5 eq.) e imidazol (1,5 eq). La mezcla se agitó a esta temperatura durante 12 horas antes de diluirse con agua. La mezcla se extrajo con Et_2O y las capas orgánicas combinadas se lavaron con H_2O y salmuera y se secaron sobre $MgSO_4$. El disolvente se retiró al vacío para dar el producto deseado. (rendimiento del 93 %). ^1H RMN (300 MHz, $CDCl_3$): δ 0,09 (s, 6 H), 0,92 (s, 9 H), 1,20 (t, J = 7,5 Hz, 3 H), 2,57 (q, J = 7,5 Hz, 2 H), 4,67 (e, 2 H), 7,29 (s, 3 H).

Etapa 2: 6-[4-[4-(terc-Butil-dimetil-silaniloximetil)-3-etil-fenil]-2-ciclopentil-2-hidroxibut-3-inil]-2,2-dimetil-[1,3]dioxin-4-ona



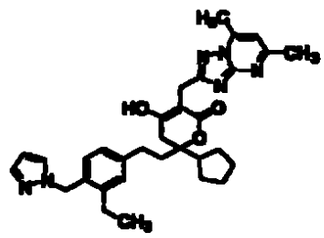
A una solución de (4-bromo-2-etil-benciloxi)-terc-butil-dimetil-silano (1,0 g, 3,05 mmol) y 6-(2-ciclopentil-2-hidroxibut-3-inil)-2,2-dimetil-4H-1,3-dioxin-4-ona (671 mg, 2,54 mmol), diisopropilamina (7 ml) y DMF (7 ml) se le añadieron $PdCl_2(PPh_3)_2$ (71 mg, 4% en moles) y CuI (14 mg, 3% en moles). La mezcla se purgó con Ar y se calentó a 90°C durante 30 min antes de enfriarse a temperatura ambiente. La reacción se diluyó con H_2O y se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con H_2O y salmuera, se secaron sobre $MgSO_4$ y se concentraron al vacío. El residuo se purificó por cromatografía en columna ultrarrápida (SiO_2, EtOAc al 5-30% en hexanos) para producir el producto deseado (1,0 g, 60% de rendimiento). ^1H RMN (300 MHz, $CDCl_3$): δ -0,10 (s, 3H), 0,00 (s, 3 H), 0,83 (s, 9 H), 1,11 (t, J = 7,5 Hz, 3 H), 1,49-1,74 (m, 8 H), 1,62 (s, 3 H), 1,64 (s, 3 H), 2,11-2,18 (m, 1H), 2,442,62 (m, 4 H), 4,63 (s, 2 H),5,37 (s, 1H), 7,08-7,13 (m, 2 H), 7,28-7,31 (m, 1H).

Etapa 3: 6-[2-ciclopentil-4-(3-etil-4-metil-fenil)-2-hidroxi-butil]-2,2-dimetil-[1,3]dioxin4-ona



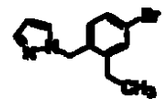
A una solución de 6-(4-[4-(terc-butil-dimetil-silaniloximetil)-3-etil-fenil]-2-ciclopentil-2-hidroxi-but-3-inil)-2,2-dimetil-[1,3]dioxin-4-ona (1,0 g) en EtOH (50 ml) se le añadió $Pd(OH)_2$ (20% en peso, 100 mg). La reacción se agitó en una atmósfera de H_2 durante 15 horas. La reacción se filtró a través de una capa de celite y el disolvente se retiró a presión reducida para producir el producto deseado. ^1H RMN (300 MHz, $CDCl_3$): δ 1,19 (t, J = 7,5 Hz, 3 H), 1,43-1,69 (m, 8 H), 1,71 (s, 6 H), 1,79-1,85 (m, 2 H), 2,05-2,16 (m, 1H), 2,27 (s, 3 H), 2,44-2,66 (m, 6 H),5,37 (s, 1H), 6,89-6,95 (m, 2 H), 7,04-7,08 (m, 1H).

Ejemplo A(112): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2 il)metil]-6-(2-[3etil-4-(1H-pirazol-1-ilmetil)fenil]etil)-4-hidroxi-5,6-dihidro-2H-piran-2-ona



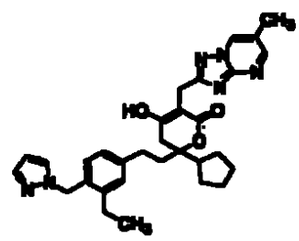
El compuesto del título se preparó de una forma análoga al ejemplo A(1), sustituyendo 1-(4-bromo-2-etilbencil)-1H-pirazol de la etapa 1 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5propoxi-benceno en la etapa 4 de ese ejemplo. ^1H RMN (400 MHz, DMSO-d_6): δ 1,11 (t, J = 7,3 Hz, 3 H), 1,48-1,80 (m, 8 H), 2,18 (m, 2 H), 2,46 (s, 3 H), 2,51-2,74 (m, 9 H), 2,89 (d, J = 17,4 Hz, 1H), 3,81 (d, J-15,9 Hz, 1H), 3,92 (d, J = 16,1Hz, 1H),5,41 (s, 2 H), 6,36 (t, J = 2,0 Hz, 1H), 6,98 (d, J = 8,3 Hz, 1H), 7,11 (m, 3 H), 7,56 (s, 1H), 7,79 (d, J = 2,1Hz, 1H), 10,95 (s, 1H).

Etapa 1: 1-(4-Bromo-2-etil-bencil)-1H-pirazol



Una solución de pirazol (616 mg, 9,1 mmol) en DMF anhidra (30 ml.) se trató con NaH (60%, 362 mg). Se añadió 4-bromo-1-bromometil-2-etil-benceno (2,5 g, 9,1 mmol) y la solución resultante se agitó a 80°C durante 13 horas antes de enfriarse a temperatura ambiente. La mezcla se diluyó con H_2O y se extrajo con Et_2O. Los extractos orgánicos combinados se lavaron con H_2O y salmuera, se secaron sobre $MgSO_4$ y se concentraron a presión reducida. El residuo se purificó por cromatografía en columna ultrarrápida para producir el producto deseado (1,92 g, 80% de rendimiento). ^1H RMN (300 MHz, $CDCl_3$): δ 1,15 (t, J = 7,5 Hz, 3 H), 2,59-2,66 (m, 2 H),5,30 (s, 2 H), 6,26-6,28 (m, 1H), 6,86-6,88 (m, 1H), 7,29-7,32 (m, 2 H), 7,37-7,38 (m, 1H), 7,54-7,55 (m, 1H).

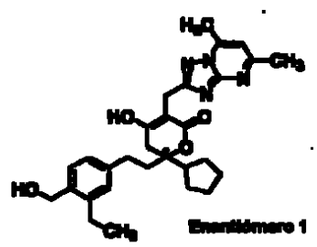
Ejemplo A(113): 6-ciclopentil-6-(2-[3-etil-4-(1H-pirazol-1-ilmetil)fenil]-etil)-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(112) sustituyendo 6metil[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído en lugar de 5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído. ^1H RMN (400 MHz, DMSO-d_6): δ 0,89 (t, J = 7,6 Hz, 3 H), 1,41-1,54 (m, 8 H), 1,89 (m, 2 H), 2,21 (s, 3 H), 2,27-2,52 (m, 6 H), 2,64 (d, J = 17,7 Hz, 1H), 3,59 (d, J = 15,9 Hz, 1H), 3,67 (d, J = 15,6 Hz, 1H),5,17 (s, 2 H), 6,12 (t, J = 15,9 Hz, 1H), 6,74 (d, J = 7,6 Hz, 1H), 6,87 (d, J = 7,8 Hz, 1H), 6,90 (d, 1H), 7,31 (s, 1H), 7,54 (d, J = 2,2 Hz, 1H), 8,53 (d, J = 2,2 Hz, 1H), 8,80 (s, 1H), 10,72 (s, 1H).

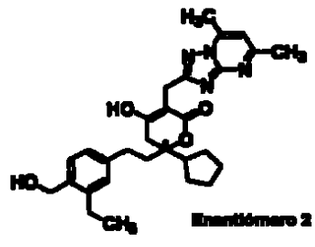
Ejemplo A(114): Enantiómero 1 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2il)metil]-6-(2-[3-etil-4-(hidroximetil)fenil]etil)-4-hidroxi-6,6-dihidro-2H-

piran-2-ona



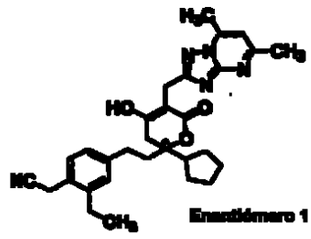
El compuesto del título se separó de la 6-ciclopentil-3-((5,7-dimetil(1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-[3-etil-4-(hidroximetil)-fenil]etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (Ejemplo B(33)) por HPLC quiral (Chiral-Pac OJ-H, 100 bar, MeOH al 30%) . t.r. =2,7 min, 100% ee.

Ejemplo A(115): Enantiómero 2 de 2 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2il)metil]-6-(2-[3-etil-4-(hidroximetil)fenil]etil)-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(3-etil-4-(hidroximetil)-fenil]etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (Ejemplo 13(33)) por HPLC quiral (Chiral-Pac OJ-H, 100 bar, MeOH al 30%) . t.r. =3,9 min, 100% ee.

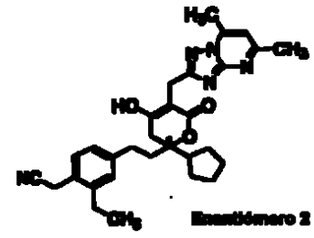
Ejemplo A(118): Enantiómero 1 de [4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]-triazolo[1,5a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-etilfenil]acetonitrilo



Enantiómero 1

El compuesto del título se separó del [4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)2-etilfenil]acetonitrilo racémico (Ejemplo A(101)) por HPLC quiral (ChiralPac AD-H, 140 bar, MeOH al 50%) . t.r. =3,4 min, 100% ee.

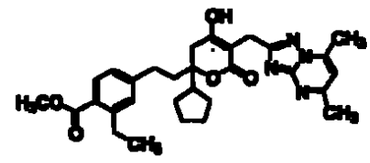
Ejemplo A(117): Enantiómero 2 de [4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]-triazolo[1,5a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilfenil]acetonitrilo



Enantiómero 2

El compuesto del título se separó del [4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)2-etilfenil]acetonitrilo racémico (Ejemplo A(101)) por HPLC quiral (ChiralPac AD-H, 140 bar, MeOH al 50%) . t.r. =4,7 min, 100% ee.

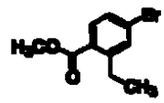
Ejemplo A(118): 4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilbenzoato de metilo



El compuesto del título se preparó de una forma análoga al ejemplo A(1) susti-

tuyendo éster metílico del ácido 4-bromo-2-etilbenzoico de la etapa 1 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,18 (t, J = 7,5 Hz, 3 H), 1,38 (s, 1H), 1,63 (m, 10 H), 2,00 (m, 2 H), 2,37 (m, 1H), 2,66 (s, 3 H), 2,72 (m, 2 H), 2,78 (s, 3 H), 2,92 (q, J = 7,4 Hz, 2 H), 3,85 (s, 3 H), 4,08 (d, J = 2,8 Hz, 2 H), 6,83 (s, 1H), 7,00 (m, 2 H), 7,75 (d, J = 7,7 Hz, 1H). HRMS calculado para $C_{30}H_{38}N_4O_5$ $(M+H)^+$: 533,2759, encontrado 533,2774,

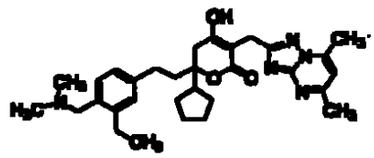
Etapa 1: éster metílico del ácido 4-bromo-2-etil-benzoico



A una solución de ácido 4-bromo-2-etil-benzoico (1,35 g,5,89 mmol) en MeOH (40 ml) se le añadió H_2SO_4 (1 gota). La mezcla se agitó a 90°C durante 48 horas, momento en el que los volátiles se retiraron al vacío. El residuo se disolvió en Et_2O, se lavó con $NaHCO_3$ saturado y salmuera, se secó sobre MgSO4 y se concentró hasta un aceite transparente (1,01g, 70%).

^{1}H RMN (300 MHz, $CDCl_3$): δ 1,22 (t, J=7,5 Hz, 3 H), 2,95 (q, J = 7,5 Hz, 2 H), 3,87 (s, 3 H), 7,36 (dd, J = 8,3, 2,1Hz, 1H), 7,42 (d, J = 2,1Hz, 1H), 7,72 (d, J = 8,3 Hz, 1H).

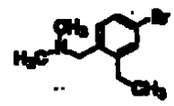
Ejemplo A(119): 6-ciclopentil-6-(2-(4-[(dimetilamino)metil]-3-etilfenil)-etil)-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo (4-bromo-2-etil-bencil)dimetil-amina de la etapa 1 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,09 (t, J = 7,5 Hz, 3 H), 1,38 (s, 1H), 1,55 (s,5 H), 1,69 (s, 2 H), 2,10 (s, 2 H), 2,49 (m, 7 H), 2,54 (s, 3 H), 2,65 (dd, J = 15,7, 8,2 Hz, 4 H), 2,74 (s, 3

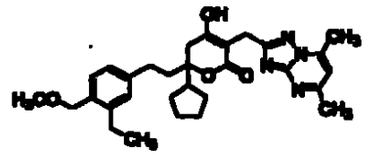
H), 2,76 (s, 3 H), 3,74 (q, J = 14,8 Hz, 2 H), 4,27 (d, J = 5,5 Hz, 2 H), 7,04 (s, 1H), 7,19 (m, 2 H), 7,35 (d, J7,7 Hz, 1H). Análisis calculado para $C_{31}H_{41}N_5O_3$.2,7 TFA: C,52,07; H,5,25; N, 8,34, Encontrado: C,51,73; H,5,56; N, 8,20.

Etapa 1: (4-Bromo-2-etil-bencil)-dimetil-amina



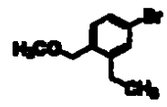
A una solución de 4-bromo-1-bromometil-2-etil-benceno (1,12 g, 4,03 mmol) en MeOH (20 ml) se le añadió dimetilamina (2,5 ml, solución al 40% en agua). La mezcla se agitó durante 1 hora, momento en el que los volátiles se retiraron al vacío. El residuo se disolvió en EtOAc, se lavó con H_2O, se secó sobre $MgSO_4$ y se concentró hasta un aceite transparente (0,910 g, 93%). ^{1}H RMN (300 MHz, CDCl3): δ 1,19 *(t, J = 7,5* Hz, 3 H), 2,21 (s, 6 H), 2,69 (q, J = 7,5 Hz, 2 H), 3,32 (s, 2 H), 7,14 (m, 1H), 7,28 (m, 2 H).

Ejemplo A(120): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2-(3etil-4-(metoximetil)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona



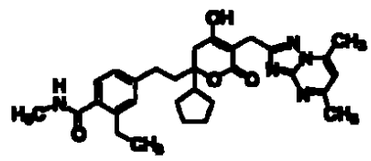
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 4-bromo-2-etil-1-metoximetil-benceno de la etapa 1 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (300 MHz, DMSO): δ 1,15 (t, J = 7,5 Hz, 3 H), 1,45 (s, 1H), 1,63 (s,5 H), 1,78 (s, 2 H), 2,05 (s, 6 H), 2,60 (m, 10 H), 3,35 (s, 3 H), 3,88 (q, J16,2 Hz, 2 H), 4,44 (s, 2 H),5,82 (s, 1H), 7,09 (d, J = 8,1Hz, 2 H), 7,24 (d, J = 7,7 Hz, 1H). Análisis calculado para $C_{30}H_{38}N_4O_4$.0,2 TFA: C, 67,43; H, 7,11; N, 10,35, Encontrado: C, 67,73; H, 7,18; N, 10,46.

Etapa 1: 4-Bromo-2-etil-1-Metoximetil-benceno



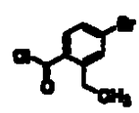
A una solución de (4-bromo-2-etil-fenil)-metanol (0,700 g, 3,25 mmol) en DMF (30 ml) se le añadió NaH (0,156 g, dispersión al 60% en aceite mineral, 3,90 mmol) seguido de MeI (0,22 ml, 3,58 mmol). La mezcla se agitó durante 16 horas y después se repartió entre H_2O y EtOAc. La capa acuosa se extrajo con EtOAc y la capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un aceite amarillo. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-40%en hexanos) dio el producto en forma de un aceite transparente (0,51g, 69%). ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,15 (t, J = 7,1Hz, 3 H), 2,58 (q, J = 7,5 Hz, 2 H), 3,32 (s, 3 H), 4,35 (s, 2 H), 7,12 (m, 1H), 7,24 (m, 1H), 7,27 (d J = 2,1Hz, 1H).

Ejemplo A(121): 4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-etil-N-metilbenzamida



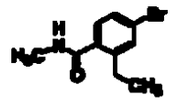
El compuesto del título se preparó de una forma análoga al ejemplo A(1), sustituyendo 4-bromo-2-etil-N-metil benzamida de la etapa 2 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (300 MHz, DMSO): δ 1,09 (t, J = 7,4 Hz, 3 H), 1,41 (s, H), 1,58 (s, 6 H), 1,72 (s, 2 H), 2,12 (d, J = 7,0 Hz, 2 H), 2,48 (m, 2H), 2,55 (s, 3 H), 2,65 (m,5 H), 2,7; (d, J = 4,3 Hz, 3 H), 2,82 (m, 1H), 3,18 (s, 2 H), 3,80 (q, J = 17,3 Hz, 2 H), 7,05 (s, 1H), 7,11 (m, 2 H) 7,21 (m, 1H), 8,10 (d, J = 4,5 Hz, 1H). Análisis calculado para $C_{30}H_{37}N_5O_4$•1,5 TFA : C,56,40; H,5,52; N, 9,97, Encontrado: C,56,68; H,5,57; N, 9,97.

Etapa 1: Cloruro de 4-bromo-2-etil-benzoílo



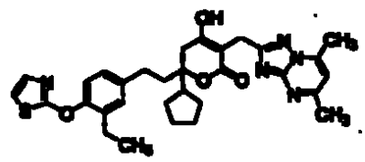
Una solución de ácido 4-bromo-2-etil-benzoico (1,72 g, 7,51 mmol) en $SOCl_2$ (50 ml) se calentó a 90°C y se agitó durante 2 horas. Los volátiles se retiraron al vacío para producir un sólido de color pardo (1,80 g 96%). ^1H RMN (300 MHz, $CDCl_3$): δ 1,22 (t, J = 7,4 Hz, 3 H), 2,89 (q, J = 7,5 Hz, 2 H), 7,49 (m, 2 H) 8,03 (d, J = 9,0 Hz, 1H).

Etapa 2: 4-Bromo-2-etil-N-metil-benzamida



A una solución de cloruro de 4-bromo-2-etil-benzoílo (1,00 g, 4,04 mmol) en CH_2Cl_2 (20 ml) se le añadió metilamina (0,70 ml, solución al 40% en agua, 8,08 mmol). La mezcla se agitó durante 3 horas, momento en el que los volátiles se retiraron al vacío. El residuo se disolvió en EtOAc, se lavó con H_2O, se secó sobre $MgSO_4$ y se concentró hasta dar un aceite de color pardo (0,8579, 88%). ^1H RMN (300 MHz, $CDCl_3$) δ 1,21 (t, J = 7,4 Hz, 3 H), 2,75 (q, J = 7,5 Hz, 2 H), 2,97 (d, J = 4,9 Hz, 3 H),5,74 (s, 1H), 7,17 (d, J = 8 Hz, 1H), 7,32 (d, J = 8,1Hz, 1H), 7,39 (s, 1H).

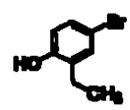
Ejemplo A(122): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6[2-[3etil-4-(1,3-tiazol-2-iloxi)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(1), sustituyendo 2-(4-bromo-2-etilfenoxi)-tiazol de la etapa 2 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5propoxi-benceno en la etapa 4 de ese ejemplo. ^1H RMN (300 MHz, DMSO): δ 1,06 (t, J = 7,4 Hz, 3 H), 1,38 (a, 1H), 1,56 (m, J = 3,4 Hz,5 H), 1,70 (s, 2 H), 2,15 (dd, J 11,2,5,0 Hz, 2 H), 2,50 (m, 10 H), 2,64 (m, 3 H), 2,81 (m, 1H), 3,79 (q, J = 7,4, 2 H), 7,04 (s, 1H), 7,19 (m,5 H). Análisis calculado para $C_{31}H_{35}N_4O_4S$•1,4 TFA: C,55,36; H,5,00; N, 9,55, Encontrado: C,55,12; H,5,11; N, 9,39.

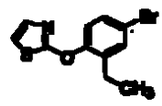
603
562

Etapa 1: 4-Bromo-2-etil-fenol



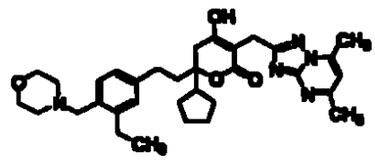
A una solución de 2-etilfenol (2,00 g, 16,4 mmol) en $CHCl_3$ (60 ml) se le añadió $TBABr_3$ (7,91 g, 16,4 mmol). La mezcla se agitó durante 20 min, momento en el que se añadieron $NaHCO_3$ saturado y $Na_2O_3S_2$ saturado. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró. La filtración a través de una capa de SiO_2 (CH_2Cl_2 al 100%) dio el producto en forma de un aceite transparente (2,3 g, 72%). ^1H RMN (300 MHz, $CDCl_3$): δ 1,22 (t, J = 7,5 Hz, 3 H), 2,60 (q, J = 7,5 Hz, 2 H), 4,71 (s, 1H), 6,64 (d, J = 8,5 Hz, 1H), 7,17 (dd, J = 8,5, 2,4 Hz, 1H), 7,25 (m, 1H).

Etapa 2: 2-(4-Bromo-2-etil-fenoxi)-tiazol



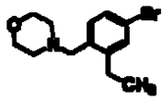
A una solución de 4-bromo-2-etil-fenol (1,00 9, 4,97 mmol) en DMF (40 ml) se le añadieron 2bromotiazol (0,341 ml, 3,82 mmol) y K_2CO_3 finamente triturado (3,17g, 22,9 mmol). La mezcla se agitó a 150°C durante 15 horas, momento en el que la solución caliente se filtró a través de un papel de filtro. El filtrado se diluyó con CH_2Cl_2 y H_2O y después se llevó a pH 6,0 con HCl 6,0 N. La capa acuosa se extrajo con CH_2Cl_2 y la capa orgánica se lavó con H_2O y salmuera. La capa orgánica se secó sobre Na_2SO_4 y se concentró para producir un aceite amarillo (1,0 g, 92%). ^1H RMN (300 MHz, $CDCl_3$): δ 1,19 (t, J-7,6 Hz, 3 H), 2,62 (q, J = 7,5 Hz, 2 H), 6,79 (d, J = 3,8 Hz, 1H), 7,10 (d, J = 8,5 Hz, 1H), 7,19 (d, J = 3,8 Hz, 1H), 7,35 (dd, J = 8,7,2,4 Hz, 1H), 7,43 (d, J = 2,4 Hz, 1H).

Ejemplo A(123): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-[3-etil-4-(morfolin-4-ilmetil)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2 ona



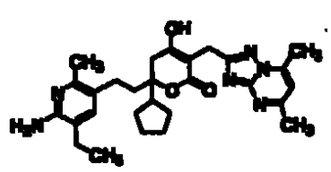
El compuesto del título se preparó de una forma análoga al ejemplo A(1), sustituyendo 4-(4-bromo-2-etil-bencil)morfolina de la etapa 1 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxibenceno en la etapa 4 de ese ejemplo. ^{1}H RMN (300 MHz, DMSO): δ 1,09 (t, J = 7,4 Hz, 3 H), 1,39 (s, 1H), 1,55 (s,5 H), 1,69 (s, 2 H), 2,10 (m, 2 H), 2,49 (s, 7 H), 2,54 (s, 3 H), 2,63 (s, 2 H), 2,75 (m, 3 H), 3,25 (s, 4 H), 3,65 (s, 1H), 3,74 (m, 2 H), 3,94 (d, J = 10,9 Hz, 2 H), 4,33 (s, 2 H), 7,04 (s, 1H), 7,19 (m, 2 H), 7,39 (d, J = 7,7 Hz, 1H). Análisis calculado para $C_{33}H_{43}N_5O_4$•2,2 TFA: C,54,47; H,5,53; N, 8,49, Encontrado: C,54,45; H,5,67; N, 8,46.

Etapa 1: 4-(4-Bromo-2-etil-bencil)-morfolina



A una solución de 4-bromo-1-bromometil-2-etil-benceno (3,67g, 13,2 mmol) en CH_3CN (66 ml) se le añadió trietilamina (2,76 ml, 19,8 mmol) y morfolina (1,38 ml, 15,8 mmol). La mezcla se agitó durante 1,5 horas, momento en el que los volátiles se retiraron al vacío para producir un sólido amarillo pálido (3,7g, 97%). ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,19 (t, J = 7,5 Hz, 3 H), 2,40 (m, 4 H), 2,68 (q, J = 7,7 Hz, 2 H), 3,40 (s, 2 H), 3,65 (m, 4 H), 7,13 (m, 1H), 7,22 (d, J = 2,1Hz, 1H), 7,30 (d, J = 2,1Hz, 1H).

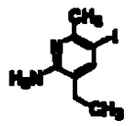
Ejemplo A(124): 6-[2-(6-Amino-5-etil-2-metilpiridin-3-il)etil]-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(1), susti-

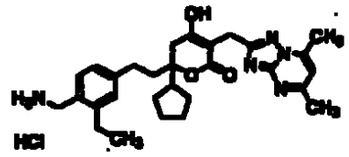
tuyendo 3-etil-5-yodo-6metil-piridin-2-ilamina de la etapa 1 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (300 MHz, DMSO): δ 1,06 (t, J = 7,3 Hz, 3 H), 1,36 (s, 1H), 1,56 (s,5 H), 1,72 (s, 2 H), 2,03 (m, 2 H), 2,27 (s, 3 H), 2,49 (m, 8 H), 2,52 (d, J = 1,5 Hz, 6 H), 3,73 (q, J = 16,2, 2 H), 7,04 (s, 1H), 7,46 (s, 2 H), 7,62 (s. 1H). HRMS calculado para $C_{28}H_{36}N_6O_3$ $(M+H)^+$: 505,2922, encontrado 505,2936,

Etapa 1: 3-etil-5-yodo-6-metil-piridin-2-ilamina



A una solución de 2-amino-3-etil-6-metilpiridina (3,00 g, 21,8 mmol) en DMF (100 ml) se le añadió N-yodosuccinimida (4,86 g, 21,8 mmol). La mezcla se agitó en la oscuridad durante 15 horas y después se repartió entre Et_2O y H_2O. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró para producir un sólido de color pardo (4,6 g, 79%). ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,19 (t, J = 7,5 Hz, 3 H), 2,35 (q, J = 7,4 Hz, 2 H), 2,49 (s, 3 H), 4,44 (s, 2 H), 7,52 (s, 1H).

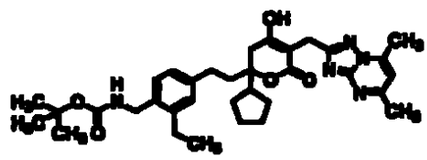
Ejemplo A(125): Hidrocloruro de 6-[2-[4-(Aminometil)-3-etilfenil]etil]-6-ciclopentil-3-[(5,7dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



Se disolvió 4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il]etil)-2-etilbencilcarbamato de terc-butilo (35 mg, 0,06 mmol, ejemplo A(126)) en diclorometano (1 ml) y HCl 4 N en dioxano (0,5 ml) y se agitó a temperatura ambiente durante 2 h. La solución se concentró para dar un sólido blanquecino (30 mg, 96%). ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,14 (t, J = 7,54 Hz, 3 H) 1,37 - 1,49 (m, 1H) 1,52 - 1,66 (m, 6 H) 1,67 - 1,77 (m, 2 H) 2,05 - 2,16 (m, 2 H) 2,58 (s, 4 H) 2,60 - 2,70 (m, 6 H) 2,74 - 2,80 (m, 1H) 3,80 (d, J = 14,51Hz, 2 H)

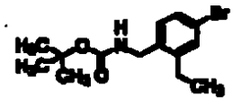
4,02 (q, J = 5,78 Hz, 2 H) 7,07 (s, 1H) 7,13 (s, 1H) 7,16 - 7,21 (m, 1H) 7,32 (d, J = 7,72 Hz, 1H) 8,15 (s, 3 H). MS (ESI): 504 $(M+H)^+$.

Ejemplo A(126): 4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-etilbencilcarbamato de terc-butilo



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo éster terc-butílico del ácido (4-bromo-2-etil-bencil)carbámico de la etapa 1 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en ese ejemplo excepto durante el tratamiento, siendo los tratamiento con HCl(ac) diluido (0,1N). ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,20 (t, 3 H) 1,40 (d, J = 6,78 Hz, 2 H) 1,45 (s, 9 H) 1,59 (d, J = 3,20 Hz, 2 H) 1,60 - 1,71 (m, 10 H) 1,88 - 1,99 (m, 2 H) 2,27 (d, J = 3,20 Hz, 2 H) 2,57 - 2,69 (m, 4 H) 2,72 - 2,80 (m, 2 H) 3,39 - 3,50 (m, 2 H) 4,30 (d, J = 4,52 Hz, 2 H) 4,59 - 4,73 (m, 1H) 6,88 - 7,01 (m. 3 H) 7,16 (d, J = 5,84 Hz, 1H). MS (ESI): 582 $(M+H)^+$

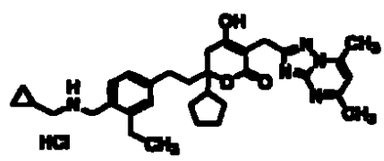
Etapa 1: Éster terc-butílico del ácido (4-bromo-2-etil-bencil)-carbámico



A una solución de 4-bromo-2-etil-bencilamina (830 mg, 3,9 mmol, de la etapa 2 del ejemplo A(131)) y trietilamina (815 µl,5,8 mmol) en THF (5 ml) a temperatura ambiente se le añadió dicarbonato de di-terc butilo (1,26 g,5,8 mmol). La solución se agitó durante 3 h, se diluyó en agua y se extrajo con acetato de etilo. La capa orgánica se lavó con bicarbonato sódico saturado y después con cloruro sódico saturado, se secó (Na_2SO_4), se filtró y se concentró *al vacío hasta dar un sólido blanquecino bruto* (1,4 g). ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,22 (t, J = 7,63 Hz, 3 H) 1,45 (s, 9 H) 2,64 (q, J = 7,54 Hz, 2 H) 4,29 (d, J = 5,65 Hz, 2 H) 4,67 (s, 1H) 7,12 (d, J = 8,10 Hz, 1H) 7,28 -

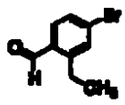
7,32 (m, 1H) 7,33 (d, J = 1,88 Hz, 1H).

Ejemplo A(127): 6-ciclopentil-6-[2-(4-{[(ciclopropilmetil)amino]metil}-3etilfenil)etil]-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6dihidro-2H-piran-2-ona



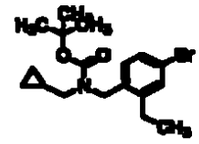
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo el éster terc-butílico del ácido (4-bromo-2-etilbencil)-ciclopropilmetil-carbámico bruto de la etapa 2 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en ese ejemplo. ^{1}H RMN (300 MHz, MeOH): δ ppm 0,40 - 0,48 (m, 2 H) 0,70 - 0,78 (m, 2 H) 1,22 (t, J = 7,54 Hz, 3 H) 1,45 - 1,57 (m, J = 7,35 Hz, 1H) 1,58 - 1,70 (m,5 H) 1,73 - 1,80 (m, J = 12,06, 4,14 Hz, 2 H) 2,06 - 2,18 (m, 2 H) 2,50 (s, 1H) 2,69 - 2,78 (m, 12 H) 3,00 (d, J = 7,54 Hz, 2 H) 3,61 - 3,68 (m, 1H) 4,02 (d, J = 3,20 Hz, 2 H) 4,24 (s, 2 H) 7,13 - 7,20 (m, 2 H) 7,36 (d, J = 7,91Hz, 1H) 7,42 (s, 1H). MS (ESI): 558 $(M+H)^+$.

Etapa 1: 4-Bromo-2-etil-benzaldehído



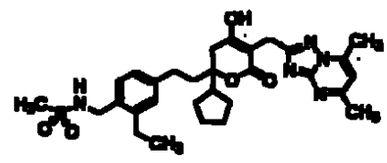
Se agitó N-óxido de morfolina (5,0 g, 43 mmol) en diclorometano (30 ml) sobre tamices moleculares de 3A durante 30 min en una atmósfera de N_2. Se añadió (4-bromo-2-etil-fenil)-metanol (3,1g, 14,4 mmol) y después perrutenato de tetrapropilamonio (250 mg, 0,72 mmol). La solución se agitó durante 2 h y después se filtró a través de una capa de sílice. La sílice se lavó con acetato de etilo al 30% en hexanos y los extractos orgánicos se combinaron. La solución se concentró al vacío para dar un aceite amarillo brillante (3,4 g). ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,28 (t, J = 7,54 Hz, 3 H) 3,04 (q, J = 7,54 Hz, 2 H) 7,47 (d, J = 1,70 Hz, 1H) 7,49 - 7,53 (m, 1H) 7,69 (d, J = 8,29 Hz, 1H) 10,23 (s, 1H).

Etapa 2: Éster terc-butílico del ácido (4-bromo-2-etil-bencil)-ciclopropilmetil-carbámico



A 4-bromo-2-etil-benzaldehído (3,0 g, 13,4 mmol) y ciclopropil metilamina (1,0 g, 14,1 mmol) en diclorometano (150 ml) se le añadió sulfato de magnesio (anhidro, 200 mg) y después cianoborohidruro sódico (2,2 g, 35 mmol). La mezcla se agitó a temperatura ambiente durante 16 h. La mezcla se diluyó en agua y se repartió. La capa orgánica se lavó con cloruro sódico saturado, se secó ($MgSO_4$), se filtró y se concentró *al vacío* hasta dar un aceite incoloro bruto (3,44 g). El residuo se disolvió de nuevo en diclorometano (100 ml) y se añadieron trietilamina (3,6 ml, 26 mmol) y después dicarbonato de di-terc-butilo (3,5 g, 16,25 mmol). La solución se agitó a temperatura ambiente durante 2 h, después se diluyó en agua y se extrajo con acetato de etilo. La capa orgánica se lavó con bicarbonato sódico saturado y después con cloruro sódico saturado, se secó (Na_2SO_4), se filtró y se concentró *al vacío* para dar éster terc-butílico del ácido (4-bromo-2-etil-bencil)-ciclopropilmetil-carbámico (3,6 g) en forma de un aceite bruto.

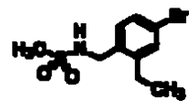
Ejemplo A(128): N-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-etilbencil]metanosulfonamida



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo N-(4-bromo-2-etilbencil)-metanosulfonamida de la etapa 1 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en ese ejemplo. ^1H RMN (300 MHz, $CDCl_3$): δ ppm 1,21 (t, J = 7,54 Hz, 3 H) 1,36 - 1,46 (m, 1H) 1,52 - 1,67

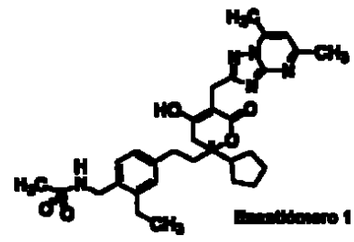
(m, 7 H) 1,96 - 2,06 (m, 2 H) 2,38 (s, 1H) 2,48 - 2,57 (m, 1H) 2,62 - 2,73 (m, 8 H) 2,79 (s, 3 H) 2,89 (s, 3 H) 4,02 - 4,15 (m, 2 H) 4,27 - 4,32 (m, 2 H) 4,32 - 4,40 (m, 1H) 5,30 (s, 1H) 6,85 (s, 1H) 6,96 - 7,03 (m, 2 H) 7,19 (d, J = 7,72 Hz, 1H). MS (ESI): 582 $(M+H)^+$.

Etapa 1: N-(4-Bromo-2-etil-bencil)-metanosulfonamida



A 4-bromo-2-etil-bencilamina (650 mg, 3 mmol) y trietilamina (500 µL, 3,6 mmol) en diclorometano (5 ml) a temperatura ambiente se les añadió cloruro de metanosulfonilo (283 µl, 3,6 mmol). La solución se agitó 1 h, se diluyó en agua y se extrajo con acetato de etilo. La capa orgánica se lavó con bicarbonato sódico saturado y después con cloruro sódico saturado, se secó (Na_2SO_4), se filtró y se concentró *al vacío* hasta dar un sólido blanquecino (880 mg, 100%). ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,25 (t, J = 7,54 Hz, 3 H) 2,69 (q, J = 7,54 Hz, 2 H) 2,90 (s, 3 H) 4,27 - 4,31 (m, 2 H) 4,40 - 4,50 (m, 1H) 7,21 (d, J = 8,10 Hz, 1H) 7,32 - 7,40 (m, 2 H).

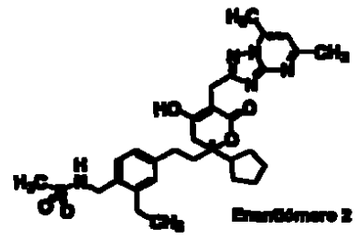
Ejemplo A(129): Enantiómero 1 de N-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-etilbencil]metanosulfonamida



El compuesto del título se separó de la N-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-etilbencil]metanosulfonamida racémica (Ejemplo A(128)) usando HPLC quiral (Chiralpak OJ-H, 120 bar, MeOH al 25%). (tiempo de retención de 4,619 min, 100% ee)

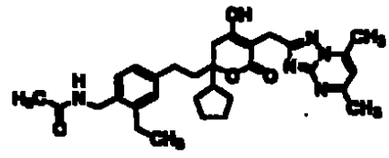
570
569

Ejemplo A(130): Enantiómero 2 de N-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilbencil]metanosulfonamida



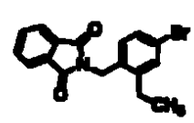
El compuesto del título se separó de la N-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilbencil]metanosulfonamida racémica (Ejemplo A(128)) usando HPLC quiral (Chiralpak OJ-H, 120 bar, MeOH al 25%). (tiempo de retención de 6,413 min, 100% ee)

Ejemplo A(131): N-[4-(2{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilbencil]acetamida



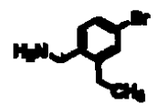
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo N-(4-bromo-2-etil-bencil)acetamida de la etapa 3 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxibenceno en ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,18 (t, J=7,54 Hz, 3 H) 1,40 (dd, J = 8,19, 6,12 Hz, 1H) 1,51 - 1,67 (m, 7 H) 1,97 - 2,05 (m, 6 H) 2,32 - 2,44 (m, 1H) 2,56 (d, J = 3,58 Hz, 1H) 2,58 - 2,73 (m, 8 H) 2,79 (s, 3 H) 4,02 - 4,15 (m, 2 H) 4,40 (d, J=5,09 Hz, 2 H) 5,51 (s, 1H) 6,85 (s, 1H) 6,94 - 7,02 (m, 2 H) 7,12 (d, J=7,72 Hz, 1H). MS (ESI): 546 $(M+H)^+$.

Etapa 1: 2-(4-Bromo-2-etil-bencil)-isoindol-1,3-diona



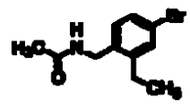
A 4-bromo-1-bromometil-2-etil-benceno (4,0 g, 14,2 mmol) en dimetilformamida (100 ml) a temperatura ambiente se le añadió ftalimida potásica (2,9 g, 15,6 mmol) y la solución se calentó a 80°C durante 5 h. La solución se enfrió a temperatura ambiente y se vertió en agua. La solución acuosa se extrajo con acetato de etilo. Los extractos orgánicos combinados se lavaron con cloruro sódico saturado, se secaron (Na_2SO_4), se filtraron y se concentraron *al vacío* hasta dar un sólido amarillo (4,0 g, 82%). ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,27 (t, J = 7,54 Hz, 3 H) 2,85 (q, J = 7,60 Hz, 2 H) 4,84 (s, 2 H) 7,14 - 7,18 (m, 1H) 7,24 - 7,27 (m, 1H) 7,34 (d, J = 2,07 Hz, 1H) 7,73 (dd, J = 5,46, 3,01Hz, 2 H) 7,86 (dd, J = 5,56, 3,11Hz, 2 H).

Etapa 2: 4-Bromo-2-etil-bencilamina



Se calentaron a reflujo 2-(4-bromo-2-etil-bencil)-isoindol-1,3-diona (4 g, 11,7 mmol) e hidrazina (1,8 ml,58,3 mmol) en cloroformo:etanol (1:1,5, 250 ml) durante 4 h. La mezcla se enfrió a temperatura ambiente y se filtró a través de una capa de celite. La solución se diluyó en agua y se repartió. La capa orgánica se lavó con agua, bicarbonato sódico saturado y después con cloruro sódico saturado, se secó (Na_2SO_4), se filtró y después se concentró *al vacío* hasta dar un aceite amarillo (2,2 g, 88%). ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,23 (t, J = 7,54 Hz, 3 H) 1,65 (s, 2 H) 2,66 (q, J = 7,60 Hz, 2 H) 3,84 (s, 2 H) 7,19 - 7,23 (m, 1H) 7,30 - 7,34 (m, 2 H).

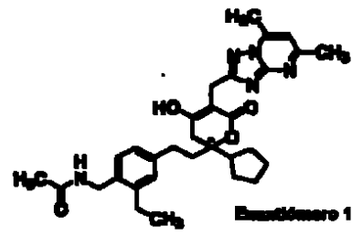
Etapa 3: N-(4-Bromo-2-etil-bencil)-acetamida



A 4-bromo-2-etil-bencilamina (700 mg, 3,3 mmol) y trietilamina (600 µl, 4,3 mmol) en diclorometano (5 ml) a temperatura ambiente se le añadió cloruro de acetilo (310 µl, 4,5 mmol). La solución se agitó durante 1 h, se diluyó en agua y se extrajo con acetato de etilo. La capa orgánica se lavó con bicarbonato sódico saturado y después

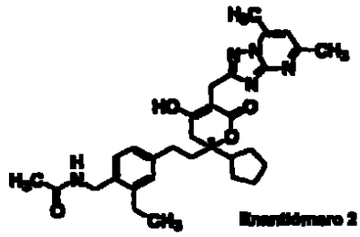
con cloruro sódico saturado, se secó (Na_2SO_4), se filtró y se concentró *al vacío* hasta dar un sólido blanquecino (820 mg, 97%). ^1H RMN (300 MHz, $CDCl_3$): δ 1,20 (t, J = 7,54 Hz, 3 H) 2,00 (s, 3 H) 2,62 (q, J = 7,54 Hz, 2 H) 4,38 (d, J = 5,46 Hz, 2 H) 5,59 (s, 1H) 7,09 (d, J = 8,10 Hz, 1H) 7,26 - 7,31 (m, 1H) 7,34 (d, J = 1,88 Hz, 1H).

Ejemplo A(132): Enantiómero 1 de N-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]-triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6,dihidro-2H-piran-2-il}etil)-2-etilbencil]acetamida



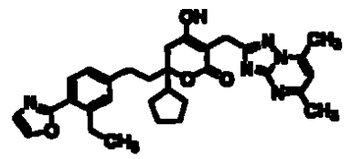
El compuesto del título se separó de la N-(4-(2{2-ciclopentil-5-((5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil)-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilbencil]acetamida racémica (Ejemplo (131)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 50%). (tiempo de retención de 4,924 min, 100% ee)

Ejemplo A(133): Enantiómero 2 de N-[4-(2-{2-ciclopentil-5-((5,7-dimetil[1,2,4]-triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilbencil]acetamida



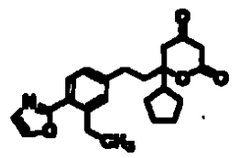
El compuesto del título se separó de la N-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-etilbencil]acetamida racémica (Ejemplo A(131)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 50%). (tiempo de retención de 6,947 min, 100% ee)

Ejemplo A(134): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2-[3-etil-4-(1,3-oxazol-2-il)fenil]etil)-4-hidroxi-5,6-dihidro-2H-piran-2-ona



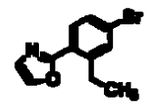
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 6-ciclopentil-6-(2-[3-etil-4 (1,3-oxazol-2-il)fenil]etil)dihidro-2H-piran-2,4(3H)-diona (Ejemplo A(135)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona en ese ejemplo. Rendimiento (35 mg, 8%). ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,19 (t, J = 7,44 Hz, 3 H) 1,50 - 1,1 (m, 3 H) 1,57 - 1,64 (m, J = 8,29 Hz, 2 H) 1,65 - 1,77 (m, 3 H) 1,99 - 2,07 (m, J = 17,33 Hz, 1H) 2,33 2,44 (m, 1H) 2,51 - 2,59 (m, 1H) 2,65 (s, 3 H) 2,68 - 2,80 (m, 7 H) 3,03 (q, J = 7,41Hz, 2 H) 4,09 (s, H) 6,83 (s, 1H) 7,03 - 7,09 (m, 2 H) 7,23 (s, 1H) 7,69 (s, 1H) 7,80 (d, J = 7,91Hz, 1H). MS (ESI): 542 $(M+H)^+$

Ejemplo A(135): 6-ciclopentil-6-(2-[3-etil-4-(1,3-oxazol-2-il)fenil]etil)-dihidro-2H-piran-2,4(3H)-diona



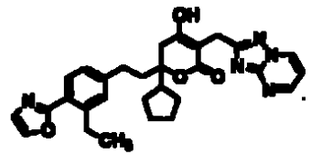
El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo 2-(4-bromo-2-etil-fenil)-oxazol de la etapa 1 mostrada a continuación en lugar de 4-bromo-2-etil-5-metoxi-piridina en la etapa 6 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,21 (t, J = 7,44 Hz, 3 H) 1,42 - 1,57 (m, 2 H 1,58 - 1,74 (m, 6 H) 1,96 - 2,04 (m, 1H) 2,14 - 2,22 (m, 1H) 2,24 - 2,35 (m, 1H) 2,67 - 2,78 (m, 2 H) 2,80 (s, 2 H) 2,89 - 2,98 (m, 2 H) 3,46 (s, 2 H) 7,11 - 7,17 (m, 2 H) 7,44 - 7,53 (m, 1H) 7,77 (d, J = 8,29 Hz, 1H) 7,84 (s, 1H). MS (ESI): 382 $(M+H)^+$

Etapa 1: 2-(4-Bromo-2-etil-fenil)-oxazol



Ácido 4-bromo-2-etil-benzoico (6,8g, 30 mmol), diisopropiletilamina (7,8 ml, 44,7 mmol), hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N;N-tetrametiluronio (HATU, 14 g, 37 mmol) y éter dimetílico de aminoacetaldehído (4 ml, 37 mmol) en 2:1 de diclorometano/dimetilformamida (120 ml) durante 5 h a temperatura ambiente. La solución se lavó con varias porciones de agua, después con HCl 1 N (ac) y cloruro sódico saturado, se secó (Na_2SO_4), se filtró y se concentró al vacío hasta dar un aceite amarillo claro bruto. El residuo se disolvió de nuevo en reactivo de Eaton (P_2O_5 en ácido metanosulfónico, 100 ml) y la solución se calentó a 135°C en una atmósfera de argón durante 6 h. La solución se enfrió a temperatura ambiente y se vertió cuidadosamente en hielo. La mezcla se extrajo con diclorometano y la capa orgánica se lavó de nuevo con cloruro sódico saturado, se secó (Na_2SO_4), se filtró y se concentró *al vacío* hasta dar un aceite bruto. El residuo se disolvió de nuevo en acetato de etilo y se lavó con bicarbonato sódico saturado y después con cloruro sódico saturado, se secó (Na_2SO_4), se filtró y se concentró al vacío hasta dar un líquido pardo puro (3,16 g, 44%). ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,24 (t, J = 7,54 Hz, 3 H) 3,09 (q, J = 7,54 Hz, 2 H) 7,27 (s, 1H) 7,42 (dd, J = 8,38, 1,98 Hz, 1H) 7,48 (d, J = 2,07 Hz, 1H) 7,74 (s, 1H) 7,81 (d, J = 8,48 Hz, 1H).

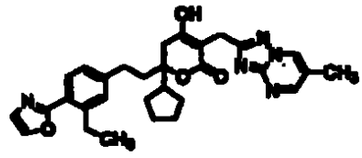
Ejemplo A(136): 6-ciclopentil-6-{2-[3-etil-4-(1,3-oxazol-2-il)fenil]etil}-4-hidroxi-3-([1,2,4]triazolo[1,5-a]pirimidin-2 il-metil)-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al Ejemplo A(1) sustituyendo 6-ciclopentil-6-{2-[3-etil-4-(1,3-oxazol-2-il)fenil]etil}dihidro-2H-piran-2,4(3H)-diona (Ejemplo A(135)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona en ese ejemplo y metoxi-[1,2,4]triazolo[1,5-a]pirimidin-2-il-metanol en lugar de 5,7-dimetil-[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído. Rendimiento (57 mg, 11%). ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,20 (t, J = 7,44 Hz, 3 H) 1,53

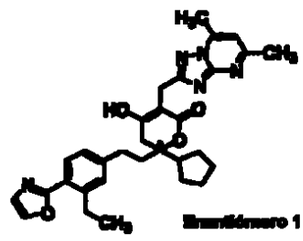
- 1,67 (m, 8 H) 2,00 - 2,11 (m, 2 H) 2,35 - 2,47 (m, 1H) 2,51 - 2,63 (m, 1H) 2,65 - 2,72 (m, 2 H) 2,72 - 2,83 (m, 2 H) 3,04 (q, J = 7,54 Hz, 2 H) 4,14 (d, J = 3,77 Hz, 2 H) 7,04 - 7,10 (m, 2 H) 7,14 - 7,20 (m, 1H) 7,25 (s, 1H) 7,71 (s, 1H) 7,82 (d, J = 7,91Hz, 1H) 8,84 (d, J = 5,46 Hz, 2 H). MS (ESI): 514 $(M+H)^+$

Ejemplo A(137): 6-ciclopentil-6-(2-[3-etil-4-(1,3-oxazol-2-il)fenil]etil)-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 6-ciclopentil-6-[2-(3-etil-4-(1,3-oxazol-2-il)fenil]etil)dihidro-2H-piran-2,4(3H)-diona (Ejemplo A(135)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona en ese ejemplo y 6-metil-[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído en lugar de 5,7dimetil-[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído. Rendimiento (58 mg, 11%). ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,19 (t, J = 7,44 Hz, 3 H) 1,40 (d, J = 4,33 Hz, 1H) 1,53 - 1,67 (m, 8 H) 2,01 - 2,10 (m, 2 H) 2,39 (s, 1H) 2,45 - 2,49 (m, 3 H) 2,54 - 2,64 (m, 1H) 2,71 (dd, J = 11,87,5,46 Hz, 2 H) 2,76 - 2,85 (m, 1H) 3,01 (q, J = 7,47 Hz, 2 H) 4,10 (s, 2 H) 7,05 - 7,11 (m, 2 H) 7,29 (s, 1H) 7,73 (s, 1H) 7,78 (d, J = 7,91Hz, 1H) 8,61 (s, 1H) 8,68 (d, *J = 2,07* Hz, 1H). MS (ESI): 528 $(M+H)^+$.

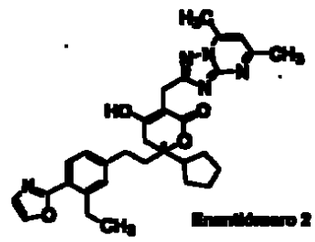
Ejemplo A(138): Enantiómero 1 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2-[3-etil-4-(1,3-oxazol-2-il)fenil]etil)-4-hidroxi-5,6-dihidro-2H-piran-2ona



El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-

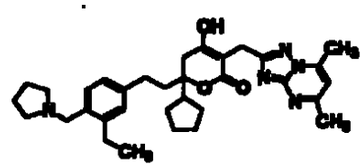
dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-[3-etil-4-(1,3-oxazol-2-il)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (Ejemplo A(134)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 50%). (tiempo de retención de 1,968 min, 100% ee)

Ejemplo A(139): Enantiómero 2 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin2-il)metil]-6-(2-[3-etil-4-(1,3-oxazol-2-il)fenil]etil)-4-hidroxi-5,6-dihidro-2H-piran-2ona



El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2-[3-etil-4-(1,3-oxazol-2-il)fenil]etil)-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (Ejemplo A(134)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 50%). (tiempo de retención de 3,537 min, 95% ee)

Ejemplo A(140): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2[3-etil-4-(pirrolidin-1-ilmetil)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona

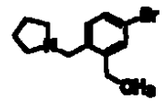


El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 1-(4-bromo-2-etilbencil)-pirrolidina de la etapa 1 mostrada a continuación en lugar de 1-benciloxi-2-etil-4-yodo-5-propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (300 MHz, DMSO): δ 1,05 (t, J = 7,3 Hz, 3 H), 1,34 (s, 1H), 1,50 (s,5 H), 1,66 (m, 2 H), 1,81 (m, 2 H), 2,02 (m, 4 H), 2,44 (m, 7 H), 2,62 (m, 7 H), 3,07 (m, 2 H), 3,37 (m, 2 H), 3,75 (q, J = 16,2 Hz, 2 H), 4,30 (d, J = 5,3 Hz, 2 H), 6,99 (s, 1H), 7,12 (m, 2 H), 7,33 (d, J = 7,7 Hz, 1H). HRMS calculado para $C_{33}H_{43}N_5O_3$ $(M+H)^+$: 558,3439, encontrado

577
576

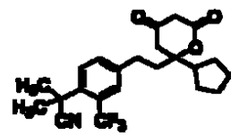
558,3446,

Etapa 1: 1-(4-Bromo-2-etil-bencil)-pirrolidina



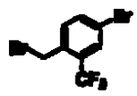
A una solución de 4-bromo-1-bromometil-2-etil-benceno (2,00 g, 7,19 mmol) en CH_2Cl_2 (30 ml) se le añadió gota a gota pirrolidina (1,19 ml, 14,4 mmol). La mezcla se agitó durante 15 horas y después se repartió entre Et_2O y H_2O. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró para producir un aceite amarillo (1,3 g, 68%). ^1H RMN (300 MHz, $CDCl_3$): δ 1,19 (t, J = 7,5 Hz, 3 H), 1,76 (m, 4 H), 2,47 (m, 4 H), 2,69 (q, J = 7,5 Hz, 2 H), 3,54 (s, 2 H), 7,19 (m, 1H), 7,25 (m, 1H), 7,29 (d, J = 1,9 Hz, 1H).

Ejemplo A(141): 2-[4-[2-(2-ciclopentil.4,6-dioxotetrahidro-2H-piran-2 il)etil]-2-(trifluorometil)fenil]-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo 2-(4-bromo-2-trifluorometilfenil)-2-metil-propionitrilo de la etapa 3 mostrada a continuación en lugar de 4-bromo-2-etil-5-metoxi-piridina en la etapa 6 de ese ejemplo. ^1H RMN (400 MHz, DMSO-d_6) δ: 1,50-1,86 (m, 14 H), 1,94-1,98 (m, 2H), 2,27-2,30 (m, 1H), 2,73-2,80 (m, 4H), 3,44 (d, J = 4,3 Hz, 2 H), 7,36 (dd, J = 8,2, 1,6 Hz, 1H), 7,54 (d , J = 1,6 Hz, 1H), 7,65 (d, J = 8,2 Hz, 1H). $(M+H)^+$MS (ESI): 422 $(M+H)^+$

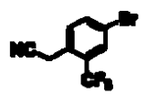
Etapa 1: 4-Bromo-1-bromometil-2-trifluorometil-benceno



Una mezcla de 4-metil-3-trifluorobromobenceno (25 9, 104,59 mmol), N-

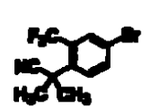
bromosuccinimida (18,62 g, 104,59 mmol) y peróxido de benzoílo (1,27 g,5,23 mmol) en CCl_4 (35 ml) se calentó a 90°C durante 4 horas. La mezcla de reacción se enfrió a 0°C y después se filtró a través de una frita de vidrio lavando con CH_2Cl2. El filtrado se concentró y después se purificó por cromatografía en columna ultrarrápida (EtOAc al 0%-5% en hexanos) para dar el producto en forma de un aceite transparente que cristalizó tras un periodo de reposo (33,26 g, 100%). ^1H RMN (400 MHz, $CDCl_3$) δ 4,57 (s, 2H), 7,46 (d, J = 8,3 Hz, 1H), 7,67 (d, J = 8,3 Hz, 1H), 7,78 (s, 1H).

Etapa 2: (4-Bromo-2-trifluorometil-fenil)-acetonitrilo



Una mezcla de 4-metil-3-trifluorobromobenceno (33,26 g, 104,261 mmol) de la etapa 1 anterior , KCN (20,43 g, 313,67 mmol) y bromuro de tetrabutilamonio (3,37 g, 10,45 mmol) en CH_2Cl_2/H_2O 1:1 (300 ml) se agitó a temperatura ambiente durante 4 horas. Las capas se separaron y la capa orgánica se lavó con H_2O (100 ml), HCl 1 N (100 ml) y salmuera, se secó sobre Na_2SO_4 y después se concentró hasta dar un aceite de color pardo que se purificó por cromatografía en columna ultrarrápida (EtOAc al 0%-20% en hexanos) para dar el producto en forma de un aceite transparente (14,9 g,54%). ^1H RMN (400 MHz, $CDCl_3$) δ 3,91 (s, 2H), 7,57 (d, J = 8,3 Hz, 1H), 7,75 (dd, J = 8,3, 2 Hz, 1H), 7,84 (d, J = 2 Hz, 1H).

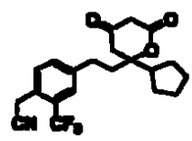
Etapa 3: 2-(4-Bromo-2-trifluorometil-fenil)-2-metil-propionitrilo



Se suspendió NaH al 95% (2,28 g, 94,7 mmol) en DMF (25 ml) y se enfrió a 0°C. Se disolvió (4-bromo2-trifluorometil-fenil)-acetonitrilo (5 g, 18,94 mmol) de la etapa 2 anterior, en THF (35 ml) y se añadió lentamente mediante una cánula a la suspensión de NaH. La mezcla de reacción se agitó durante 20 minutos, se añadió yoduro de metilo (11,79 ml, 189,36 mmol) y la mezcla resultante se agitó durante una noche a temperatura ambiente. La reacción se interrumpió con H_2O (100 ml). Los disolventes se retiraron al vacío y el residuo se repartió entre EtOAc y HCl 1 N (100 ml). La fase orgánica

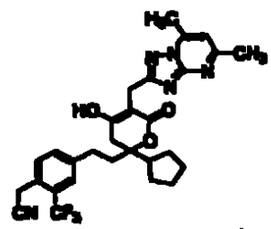
se secó sobre Na_2SO_4 y se evaporó. El producto orgánico bruto se purificó por cromatografía en columna ultrarrápida (EtOAc al 5% en hexanos) para dar el producto (4,14 g, 75%) en forma de un aceite transparente. ^1H RMN (400 MHz, $CDCl_3$) δ 1,6 (s, 6H), 7,46 (d, J = 8,3 Hz, 1H), 7,67 (d, J = 8,3 Hz, 1H), 7,78 (s, 1H).

Ejemplo A(142): [4[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil-2-(trifluorometil)fenil]acetonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo 4-bromo-1-bromometil-2-trifluorometil-benceno de la etapa 2 del ejemplo A(141) en lugar de 4-bromo-2-etil-5-metoxi-piridina en la etapa 6 de ese ejemplo. ^1H RMN (400 MHz, $CDCl_3$) δ: 1,48-1,62 (m a, 8 H), 1,94-1,97 (m, 2H), 2,24-2,30 (m, 1H), 2,69-2,84 (m, 4 H), 3,44 (d, J = 4,04 Hz, 2 H), 3,92 (s, 2H), 7,40 (d, J = 8,08 Hz, 1H), 7,47 (s, 1H), 7,60-7,62 (m, 1H). MS (ESI): 394 $(M+H)^+$

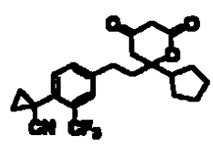
Ejemplo A(143): (4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-(trifluorometil)fenil]acetonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo [4[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-(trifluorometil)fenil]-acetonitrilo (ejemplo A(142)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4diona de ese ejemplo. ^1H RMN (400 MHz, DMSO-d_6) δ: 1,38-1,74 (m a, 10 H), 2,13-2,23 (m, 1H), 2,49-2,58 (m, 7 H), 2,73-2,87 (m, 3H), 3,76 (d, J = 16 Hz, 1H), 3,85 (d, J = 16 Hz, 1H), 4,16 (s, 2H), 7,06 (s, 1H), 7,64-7,77 (m, 3H), 10,87

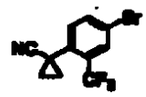
(s, 1H). Análisis calculado para $C_{28}H_{30}F_3N_5O_3.0,5\ H_2O$: C, 61,91; H,5,55, N, 12,45; Encontrado: C, 62,00; H,5,85, N, 12,65, MS (ESI): 554,1 $(M+H)^+$.

Ejemplo A(144): 1-[4[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-(trifluorometil)fenil]ciclopropanocarbonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo 1-(4-bromo-2-trifluorometilfenil)-ciclopropanocarbonitrilo de la etapa 1 mostrada a continuación en lugar de 4-bromo-2-etil-5-metoxi-piridina en la etapa 6 de ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$) δ:1,41-1,43 (m, 2H), 1,531,77 (m, 10 H), 1,93-1,97 (m, 2H), 2,25-2,30 (m, 1H), 2,72-2,80 (m, 4H), 3,44 (d, J = 4,8 Hz, 2 H), 7,33-7,35 (m, 1H), 7,47-7,49 (m, 2 H). MS (ESI): 420 $(M+H)^+$.

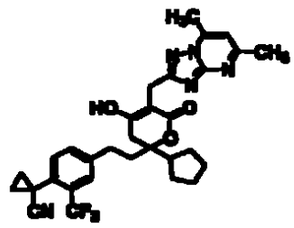
Etapa 1: 1-(4-Bromo-2-trifluorometil-fenil)-ciclopropanocarbonitrilo



A una solución agitada de (4-bromo-2-trifluorometil-fenil)-acetonitrilo (3,33 g, 12,61 mmol) de la etapa 2 del ejemplo A(141), cloruro de bencitrietilamonio (0,057 g, 0,25 mmol) y 1-bromo-2-cloroetano (1,57 g, 10,94 mmol), se le añadió gota a gota una solución de NaOH al 40% (3 ml). La mezcla de reacción se agitó durante 6 horas a 50°C. Después de este tiempo, la reacción se interrumpió con HCl 1 N (30 ml) y se extrajo con EtOAC (3 x 30 ml). La fase orgánica se secó sobre Na_2SO_4 y se evaporó. El producto orgánico bruto se purificó por cromatografía en columna ultrarrápida (EtOAc al 10% en hexanos) para dar el producto (3,1 g, 86%) en forma de un aceite transparente. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,4-1,44 (m, 2H), 1,76-1,80 (m, 2H), 7,44 (d, J = 8,3 Hz, 1H), 7,69 (dd, J = 8,3, 2 Hz, 1H), 7,84 (d, J = 2 Hz, 1H).

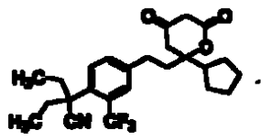
Ejemplo A(145): 1-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6,dihidro-2H-piran-2-il)etil)-2-

(trifluorometil)fenil]ciclopropanocarbonitrilo



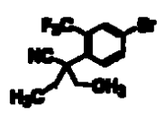
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 1-[4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-(trifluorometil)fenil]-ciclopropanocarbonitrilo (ejemplo A(144)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil)dihidro-piran-2,4-diona de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,86-0,90 (m, 2H), 1,271,79 (m, 12 H), 2,11-2,16 (m, 1H), 2,48-2,59 (m, 7 H), 2,76-2,80 (m, 3H), 3,75 (d, J = 16 Hz, 1H), 3,86 (d, J = 16 Hz, 1H), 7,07 (s, 1H), 7,65-7,70 (m, 3H), 10,87 (s, 1H). Análisis calculado para $C_{31}H_{32}F_3N_5O_3$.1,0 H_2O: C, 62,30; H,5,73, N, 11,72; Encontrado: C, 62,40; H,5,85, N, 11,90, MS (ESI): 580,1 $(M+H)^+$

Ejemplo A(146): 2-[4-[2-2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-(trifluorometil)fenil]-2-etilbutanonitrilo



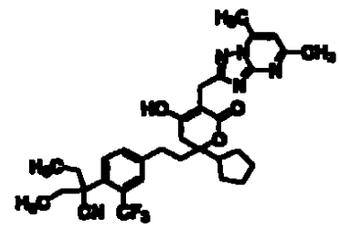
El compuesto del título se preparó de una forma análoga al ejemplo A(2) sustituyendo 2-(4-bromo-2-trifluorometilfenil)-2-etil-butironitrilo de la etapa 1 mostrada a continuación en lugar de 4-bromo-2-etil-5-metoxipiridina en la etapa 6 de ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$) δ: 0,95 (t, J = 7,2 Hz, 6 H), 1,45-1,78 (m, 8 H), 1,96-2,31 (m, 7 H), 2,74-2,80 (m, 4 H), 3,44 (d, J = 3,03 Hz, 2 H), 7,35 (dd, J = 8,08, 1,77 Hz, 1H), 7,56 (s, 1H), 7,70 (d, J = 8,08, Hz 1H). MS (ESI): 450 $(M+H)^+$.

Etapa 1: 2-(4-Bromo-2-trifluorometil-fenil)-2-etil-butironitrilo



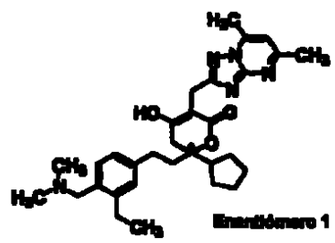
El compuesto del título se preparó de una forma análoga a la etapa 3 del ejemplo A(141) sustituyendo yodoetano en lugar de yoduro de metilo en ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,75 (t, J = 7,2 Hz, 6 H), 1,3-1,4 (m, 4H), 7,46 (d, J = 8,3 Hz, 1H), 7,67 (d, J = 8,3 Hz, 1H), 7,78 (s, 1H).

Ejemplo A(147): 2-[4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-(trifluorometil)fenil]-2-etilbutanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 2-(4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-(trifluorometil)fenil]-2-etilbutanonitrilo (ejemplo A(146)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]dihidro-piran-2,4-diona de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,77 (t, J = 7,2 Hz, 6 H), 1,28-1,62 (m, 10 H), 1,90-2,10 (m,5 H), 2,36-2,50 (m, 7 H), 2,58-2,74 (m, 3H), 3,62 (d, J = 16 Hz, 1H), 3,74 (d, J = 16 Hz, 1H), 6,97 (s, 1H), 7,58-7,67 (m, 3H), 10,77 (s, 1H). MS (ESI): 610 $(M+H)^+$.

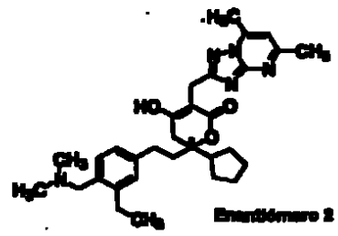
Ejemplo A(148): Enantiómero 1 de 6-ciclopentil-6-(2-(4-[(dimetilamino)metil]-3-etilfenil)etil)-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se separó de la 6-ciclopentil-6-(2-(4[(dimetilamino)metil]-

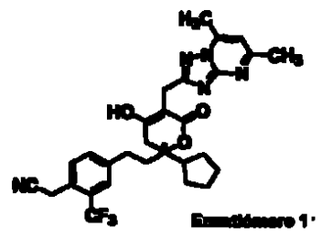
3-etilfenil)etil)-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (238 mg, Ejemplo A(119)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 35% en peso/ trietilamina al 0,1%). (31.7 mg, tiempo de retención 2,108 min, 100% ee)

Ejemplo A(149): Enantiómero 2 de 6-ciclopentil-6-(2-(4-((dimetilamino)metil]-3-etilfenil)etil)-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se separó de la 6-ciclopentil-6-(2-[4-[(dimetilamino)metil]-3-etilfenil)etil)-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (238 mg, Ejemplo A(119)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 35% en peso/ trietilamina al 0,1%). (20,7 mg, tiempo de retención 3,754 min, 100% ee).

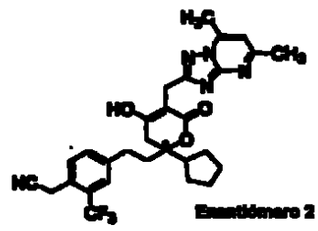
Ejemplo A(150): Enantiómero 1 de [4-(2-[2-Ciclopentil-5-[(5,7-dimetil[1,2,4]-triazolo[1,5a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-(trifluorometil)fenil]acetonitrilo



El compuesto del título se separó del [4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-(trifluorometil)fenil]acetonitrilo racémico (490 mg, Ejemplo A(143)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 50%). (100 mg, tiempo de retención

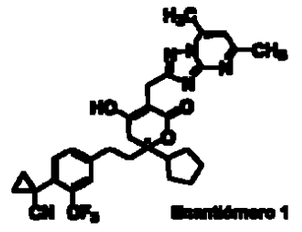
1,64 min, 100% ee)

Ejemplo A(151): Enantiómero 2 de [4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]-triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-(trifluorometil)fenil]acetonitrilo



El compuesto del título se separó del [4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-(trifluorometil)fenil]acetonitrilo racémico (490 mg, Ejemplo A(143)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 50%). (75 mg, tiempo de retención 3,67 min, 100% ee)

Ejemplo A(152): Enantiómero 1 de 1-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]-triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-(trifluorometil)fenil]ciclopropanocarbonitrilo

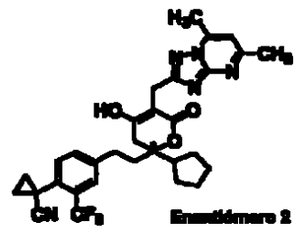


El compuesto del título se separó del 1-[4-(2-(2-ciclopentil-5-((5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-(trifluorometil)fenil]ciclopropanocarbonitrilo racémico (250 mg, Ejemplo A(145)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 50%). (95 mg, tiempo de retención 1,66 min, 100% ee)

Ejemplo A(153): Enantiómero 2 de 1-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]-

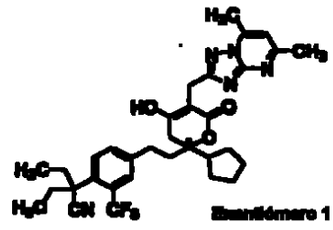
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triazolo[1,5a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-(trifluorometil)fenil]ciclopropanocarbonitrilo



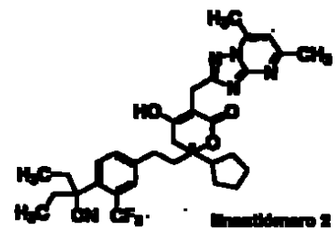
El compuesto del título se separó del 1-[4-(2-[2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-(trifluorometil)fenil]ciclopropanocarbonitrilo racémico (250 mg, Ejemplo A(145)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 50%). (87 mg, tiempo de retención 5,38 min, 100% ee)

Ejemplo A(154): Enantiómero 1 de 2-[4[2-[2-ciclopentil-5-[(5,7-dimetil[1,2,4]-triazolo[1,5a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-(trifluorometil)fenil]-2-etilbutanonitrilo



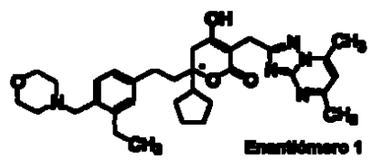
El compuesto del título se separó del 2-[4-(2-[2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-(trifluorometil)fenil]-2-etilbutanonitrilo racémico (180 mg, Ejemplo A(147)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 30%). (62.27 mg, tiemp de retención 2,47 min, 100% ee)

Ejemplo A(155): Enantiómero 2 de 2-[4-(2-[2-ciclopentil-5-[(5,7-dimetil[1,2,4]-triazolo[1,5a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-(trifluorometil)fenil]-2-etilbutanonitrilo



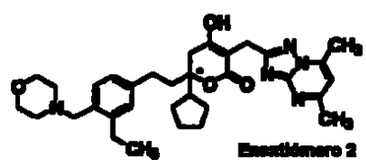
El compuesto del título se separó del 2-[4-(2{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-(trifluorometil)fenil]-2-etilbutanonitrilo racémico (180 mg, Ejemplo A(147)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 30%). (180 mg, tiempo de retención 7,57 min, 100% ee)

Ejemplo A(156): Enantiómero 1 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-[3-etil-4-(morfolin-4-ilmetil)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2ona



El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-[3-etil-4-(morfolin-4-ilmetil)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (151 mg, Ejemplo A(123)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 40%). (32 mg, tiempo de retención 3,302 min, 100% ee)

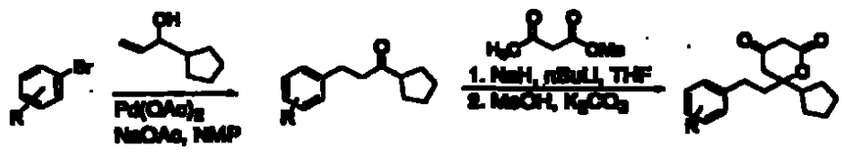
Ejemplo A(157): Enantiómero 2 de 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-{2-[3-etil]-4-(morfolin-4-ilmetil)fenil]etil}-4-hidroxi-5,6-dihidro-2H-piran-2ona



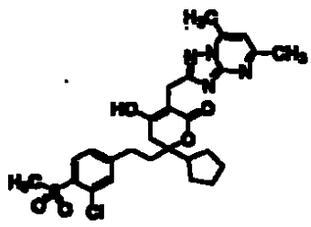
586

El compuesto del título se separó de la 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2-[3-etil-4-(morfolin-4-ilmetil)fenil]etil)-4-hidroxi-5,6-dihidro-2H-piran-2-ona racémica (151 mg, Ejemplo A(123)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 40%). (34 mg, tiempo de retención 9,004 min, 100% ee)

Esquema 2: Ruta de Heck

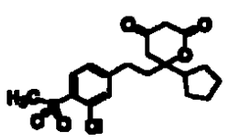


Ejemplo B(1): 6-(2-[3-cloro-4-(metilsulfonil)feniletil)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil-4-hidroxi-5,6-dihidro-2H-piran-2-ona



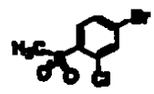
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 6-(2-[3-cloro-4-(metilsulfonil)fenil]etil)-6-ciclopentildihidro-2H-piran-2,4(3H)-diona (Ejemplo B(2)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4diona en ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,45-2,22 (m, 11H), 2,56 (s, 3 H), 2,70-2,99 (m, 7 H), 3,02 (m, 2 H), 3,26 (s, 3H), 6,99 (s, 1H), 7,01 (s, 1H), 7,25 (s, 1H), 7,36 (m, 2 H). Análisis calculado para $C_{27}H_{31}N_4O_6S$: C,58,01; H,5,59; N, 10,02, Encontrado: C,58,05; H,5,50; N, 9,89.

Ejemplo B(2): 6-(2-[3-cloro-4-(metilsulfonil)feniletil)-6-ciclopentil-dihidro-2H-piran-2,4(3H)-diona



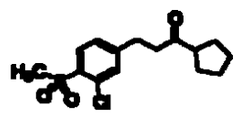
Se añadió acetoacetato de metilo (1,03 ml, 9,5 mmol) a una suspensión enfriada a 0°C de NaH (0,38 g, 9,5 mmol, dispersión al 60% en aceite mineral) en THF (30 ml). Después de 15 minutos, se añadió n-BuLi (3,8 ml, 9,5 mmol, 2,5M en hexanos). El dianión resultante se agitó durante 30 minutos más y después se trató con una solución de 3-(3-cloro-4-metanosulfonil-fenil)-1-ciclopentil-propan-1-ona (1,0 g, 3,18 mmol, de la etapa 2 mostrada a continuación) en THF (20 ml). Después de agitar durante 30 minutos a 0°C y después a temperatura ambiente durante 2 horas, la mezcla de reacción se inactivó con HCl 1 N y se extrajo con EtOAc. Las capas orgánicas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron hasta dar un aceite amarillo que se usó sin purificación adicional. El aceite se disolvió en metanol (100 ml), se trató con carbonato potásico (1,0 g, 7,2 mmol) y se calentó a reflujo en una atmósfera de N_2 durante 60 minutos. La mezcla de reacción se repartió entre H_2O e IPE. La capa acuosa se acidificó con HCl 1 N y se extrajo con EtOAc. Las capas orgánicas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron para dar el producto (0,9 g, 71% de rendimiento). ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,25-2,30 (m, 11H), 2,75-3,16 (m, 6 H), 3,26 (s, 3H), 7,21 (s, 1H), 7,40 (m, 2 H)

Etapa 1: 4-Bromo-2-cloro-1-metanosulfonil-benceno



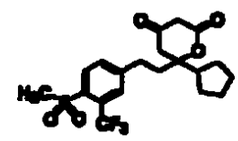
Se añadió hidrazina monohidrato (1,51 ml, 48 mmol) a una solución enfriada a 0°C de cloruro de 4-bromo-2-clorobencenosulfonilo (5 g, 17,2 mmol) disuelto en THF (50 ml). La reacción se agitó a temperatura ambiente durante 2 horas y después el disolvente se retiró al vacío para dar un sólido blanco. El sólido se disolvió en EtOH (100 ml) y se trató con acetato sódico (6,56 g, 80 mmol) seguido de yoduro de metilo (4,9 ml, 79 mmol). La mezcla de reacción se calentó a reflujo durante 18 horas. El disolvente se retiró al vacío para dar un residuo que se repartió entre HCl 1 N y EtOAc. La capa orgánica se secó sobre $MgSO_4$ y se concentró. La mezcla bruta se purificó por cromatografía en columna ultrarrápida para dar el producto (1,5 g, 32%). ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,26 (s, 3 H), 7,63 (dd, J = 8,5, 1,9 Hz, 2 H), 7,74 (d, J = 1,9 Hz, 1H), 8,02 (d, J = 8,5 Hz, 1H).

Etapa 2: 3-(3-cloro-4-metanosulfonil-fenil)-1-ciclopentil-propan-1-ona



Una mezcla de 4-bromo-2-cloro-1-metanosulfonil-benceno (1,5 g,5,6 mmol), 1-ciclopentil-2-propen1-ol (0,88 g, 6,96 mmol) y acetato sódico (0,57 g, 6,9 mmol) en DMAC (20 ml) se purgó con N_2 durante 30 minutos. Se añadió acetato de paladio (II) (25 mg, 0,11 mmol) y la mezcla se calentó a 90°C en una atmósfera de N_2 durante 16 horas. La mezcla de reacción se repartió entre HCl 1 N y EtOAc. Las capas orgánicas se lavaron con $NaHCO_3$ saturado y salmuera, se secaron sobre Na_2SO_4 y se concentraron hasta dar un aceite de color pardo. La purificación por cromatografía en columna ultrarrápida (EtOAc al 0%-20% en hexanos) dio el producto deseado (1,2 g, 69%). ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,56-1,85 (m a, 8 H), 2,83 (m, 3 H), 2,96 (t, J = 7,5 Hz, 2 H), 3,25 (s, 3 H), 7,29 (dd, J = 8,1, 1,5 Hz, 1H), 7,39 (d, J = 1,5 Hz, 1H), 8,04 (d, J = 8,1Hz, 1H).

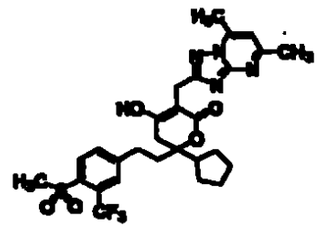
Ejemplo B(3): 6-ciclopentil-6-(2-[4-(metilsulfonil)-3-(trifluorometil)fenil]-etil)dihidro-2H-piran-2,4(3H)-diona



El compuesto del título se preparó de una forma análoga al ejemplo B(2) sustituyendo 4-bromo-1metanosulfonil-2-trifluorometil-benceno en lugar de cloruro de 4-bromo-2-clorobencenosulfonilo en la etapa 1 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,50-2,40 (m, 11H), 2,80-3,46 (m, 9 H), 7,52 (d, J = 1,56 Hz, 1H), 7,78 (s, 1H), 7,90 (d, J = 1,08 Hz, 1H).

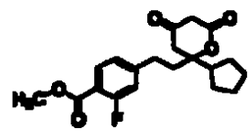
Ejemplo B(4): 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-(2-[4-(metilsulfonil)-3-(trifluorometil)fenil]etil)-5,6-dihidro-2H-piran-2-ona

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589



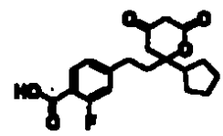
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 6-ciclopentil-6-[2-[4-(metilsulfonil)-3-(trifluorometil)fenil]etil]dihidro-2H-piran-2,4(3H)-diona (Ejemplo B(3) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxifenil)-etil]-dihidro-piran-2,4-diona en ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,35-2,19 (m, 11H), 2,40 (m,5 H), 2,73 (m,5 H), 3,04 (t, J = 12,57 Hz, 2 H), 3,13 (s, 3 H), 7,03 (s, 1H), 7,52 (d, J = 1,52 Hz, 1H), 7,80 (s, 1H), 7,90 (d, J = 2,56 Hz, 1H) Análisis calculado para $C_{28}H_{31}N_4O_8SF_3$: C,56,74; H,5,27; N, 9,45, Encontrado: C,56,50; H,5,40; N, 9,04.

Ejemplo B(5): 4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-fluorobenzoato de metilo



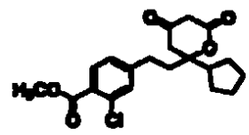
El compuesto del título se preparó de una forma análoga al ejemplo B(2) sustituyendo éster metílico del ácido 4-bromo-2-fluorobenzoico en lugar de cloruro de 4-bromo-2-clorobencenosulfonilo en la etapa 1 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,38-2,30 (m, 11H), 2,60-3,15 (m, 6 H), 3,88 (s, 3 H), 6,91 (d, J = 7,91Hz, 1H), 7,17 (m, 1H), 7,93 (d, J = 7,56 Hz, 1H)

Ejemplo B(6): Ácido 4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-fluorobenzoico



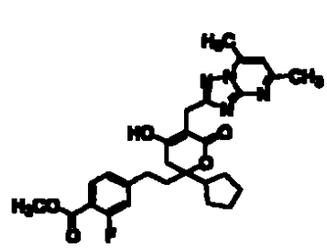
Se trató 4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-fluorobenzoato de metilo (ejemplo B(5)) (300 mg) con NaOH 4 N (10 ml) y se agitó durante 4 horas a temperatura ambiente. La mezcla después se acidificó con HCl 1 N (20 ml) y el producto se extrajo con acetato de etilo (2x20 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio y se concentraron hasta dar un sólido. El sólido se recristalizó en éter dietílico para producir el compuesto del título en forma de un sólido blanco (120 mg). ^{1}H RMN (300 MHz, MeOD): δ 1,38-2,30 (m, 11H), 2,80-3,12 (m, 6 H), 6,91 (d, J = 7,19 Hz, 1H), 7,17 (m, 1H), 7,86 (d, J = 719 Hz, 1H)

Ejemplo B(7): 2-cloro-4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]benzoato de metilo



El compuesto del título se preparó de una forma análoga al ejemplo B(2) sustituyendo éster metílico del ácido 4-bromo-2-clorobenzoico en lugar de cloruro de 4-bromo-2-clorobencenosulfonilo en la etapa 1 de ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,38-2,30 (m, 11H), 2,78-3,15 (m, 6 H), 3,98 (s, 3 H), 7,10 (s, 1H), 7,19 (d, J = 1,58 Hz, 1H), 7,62 (d, J = 1,58 Hz, 1H)

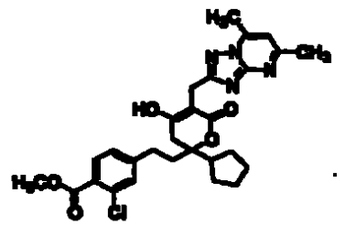
Ejemplo B(8): 4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorobenzoato de metilo



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-fluorobenzoato de metilo (ejemplo B(5)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona en ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,25-1,85 (m, 8

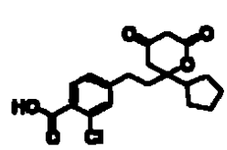
H), 2,01-1,10 (m, 3 H), 2,58-2,80 (m, 10 H), 3,10 (t, J = 12,57 Hz, 1H) 3,88 (s, 3 H), 6,91 (d, J = 2,57 Hz, 1H) 6,99 (s, 1H), 7,15 (d, J = 1,58 Hz, 1H), 7,92 (m, 1H) Análisis calculado para $C_{28}H_{37}N_4O_5F$: C, 64,36; H,5,98; N, 10,72, Encontrado: C, 64,50; H,5,40; N, 10,70.

Ejemplo B(9): 2-cloro-4-(2-[2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo-[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)benzoato de metilo



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 2-cloro-4-[2-(2ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]benzoato de metilo B(7)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona en ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,25-1,85 (m, 8 H), 2,01-1,10 (m, 3 H), 2,58-2,80 (m, 10 H), 3,10 (t, J = 12,57 Hz, 1H) 3,88 (s, 3 H), 6,91 (d, J = 2,57 Hz, 1H) 6,99 (s, 1H), 7,10 (s, 1H), 7,19 (d, J = 1,8 Hz, 1H), 7,62 (d, J = 1,56 Hz, 1H)

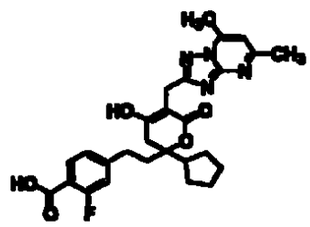
Ejemplo B(10): ácido 2-cloro-4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]benzoico



El compuesto del título se preparó de una forma análoga al ejemplo B(6): sustituyendo 2-cloro-4-[2-(2ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]benzoato de metilo (ejemplo 8(7)) en lugar de 4[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-fluorobenzoato de metilo en ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,38-2,30 (m, 11H), 2,78-3,15 (m, 6 H), 7,10 (s, 1H), 7,19 (d, J = 1,58 Hz, 1H), 7,62 (d, J = 1,56 Hz, 1H) 12,30 (s, 1H).

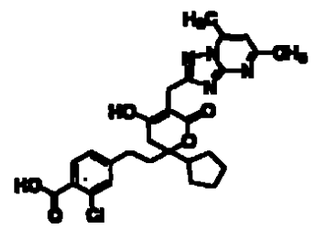
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Ejemplo B(11): Ácido 4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-fluorobenzoico



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo ácido 4-(2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-fluorobenzoico (Ejemplo B(6): en lugar de 6ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona en ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,25-1,85 (m, 8 H), 2,01-1,10 (m, 3 H), 2,58-2,80 (m, 10 H), 3,10 (t, J = 12,57 Hz, 1H), 6,94 (d, J = 2,57 Hz, 1H) 6,99 (s, 1H), 7,20 (d, J = 8,29 Hz, 1H), 7,90 (m, 1H)

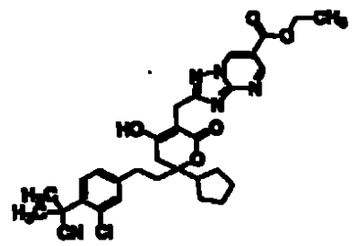
Ejemplo B(12): Ácido 2-cloro-4-(2-[2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)benzoico



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo ácido 2-cloro-4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]benzoico (ejemplo B(10)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona en ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,25-1,85 (m, 8 H), 2,01-1,10 (m, 3 H), 2,58-2,80 (m, 10 H), 3,10 (t, J = 12,57 Hz, 1H), 6,99 (s, 1H), 7,10 (s, 1H), 7,22 (d, J = 7,26 Hz, 1H), 7,60 (d, J = 7,56 Hz, 1H)

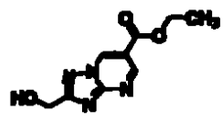
Ejemplo B(13): 2-[(6-[2-[3-cloro-4-(1-ciano-1-metiletil)feniletil)-6-ciclopentil-4-

hidroxi-2-oxo-5,6-dihidro-2H-piran-3-il)metil][1,2,4]triazolo[1,5-a]pirimidina-6-carboxilato de etilo



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 2-(2-cloro-4-[2-(2-ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]-fenil)-2-metil-propionitrilo de la etapa 5 del ejemplo 13(22) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)etil)-dihidro-piran-2,4-diona y éster etílico del ácido 2-formil-[1,2,4]triazolo[1,5-]pirimidina-6-carboxílico de la etapa 2 mostrada a continuación en lugar de 2,5-dimetil-2H-[1,2,4]triazol-3-carbaldehído en ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,36 (t, J = 7,56, Hz, 3 H) 1,42-1,68 (m, 8 H), 1,85 (e, 6 H), 2,00-2,25 (m,5 H), 3,24-3,48 (m,5 H), 4,24 (q, J = 12,06 Hz, 2 H), 6,89-7,39 (m,5 H). Análisis calculado para $C_{31}H_{34}ClN_5O_5$: C, 62,89; H,5,79; N, 11,83, Encontrado: C, 62,94; H,5,73; N, 11,48.

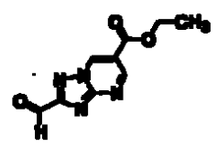
Etapa 1: Éster etílico del ácido 2-hidroximetil-[1,2,4]triazolo[1,5]pirimidina-6-carboxílico



Se mezcló 5-amino-1H-[1,2,4]triazol-3-il)-metanol (Bru-Magniez et al US (1995) documento US 5387747 A19950207) (7,9 g, 41,6 mmol) con éster etílico del ácido 2-formil-3-oxo-propiónico (Tom Sigeri et al Synthesis (1986) 5 páginas 400-402), (6,0 g, 41,6 mmol) en ácido acético (30 ml). La mezcla de reacción se calentó a 60°C durante 18 horas. Después de este tiempo, la mezcla se enfrió a temperatura ambiente y se diluyó con éter dietílico (200 ml). El producto precipitó de la solución. Después, los sólidos se filtraron y se lavaron con éter dietílico (200 ml), el producto se secó en una estufa de vacío durante 5 horas para producir el compuesto del título en forma de un sólido

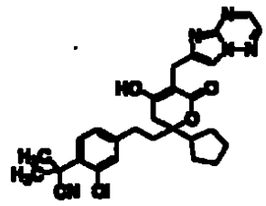
blanco (8,0 g). ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,47 (t, J = 6,97, Hz, 3 H) 3,00 (s a, 1H) 4,53 (q, J = 7,16 Hz, 2 H),5,00 (s, 2 H) 9,40 (d, J = 2,07, Hz, 1H) 9,50 (d, J = 2,07, Hz, 1H)

Etapa 2: Éster etílico del ácido 2-formil-[1,2,4]triazolo[1,5-]pirimidina-6-carboxílico



Se mezció éster etílico del ácido 2-hidroximetil-[1,2,4]triazolo[1,5]pirimidina-6-carboxílico (1,0 g, 4,5 mmol) con TEMPO (75 mg, 7,5% en peso) y se añadió $PhI(OAc)_2$ (1,59 g, 4,95 mmol) en diclorometano (7,5 ml). La reacción se agitó a temperatura ambiente durante 18 horas, tiempo después del cual la reacción se purificó por cromatografía en columna ultrarrápida (EtOAc al 0%-700% en hexanos) dio el producto en forma de un sólido blanco (800 mg.). ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,42 (t, J = 6,97, Hz, 3 H), 4,48 (q, J = 6,97 Hz, 2 H),5,00 (s, 2 H) 9,39 (d, J = 2,26, Hz, 1H) 10,12 (d, J = 2,26, Hz, 1H), 10,20 (s, 1H).

Ejemplo B(14): 2-(2-cloro-4-(2-[2-ciclopentil-4-hidroxi-5-(imidazo[1,2-b][1,2,4]triazin-6-ilmetil)-6-oxo-3,6-dihidro-2H-piran-2-il]etil)fenil)-2-metilpropanonitrilo

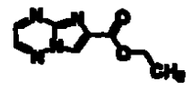


Se preparó de una forma análoga al ejemplo A(1) sustituyendo imidazo[1,2-b][1,2,4]triazina-6-carbaldehído (47 mg, 0,34 mmol, de la etapa 2 mostrada a continuación) en lugar de 5,7-dimetil-[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído y 2-(2-cloro-4-[2-(2-ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]-fenil)-2metil-propionitrilo (87 mg, 0,22 mmol de la etapa 5 del ejemplo B(22)) en lugar de 6-ciclopentil-6-[2-(5etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona. Rendimiento 10 mg, 8.7%. ^{1}H RMN

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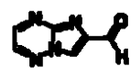
(400 MHz, $CDCl_3$) δ 1,24-1,74 (m, 8 H), 1,83 (s, 6 H), 1,98-2,02 (m, 2 H), 2,39 (t, J = 8,84 Hz, 1H), 2,50 (d, J = 17,68 Hz, 1H), 2,63-2,71 (m, 2 H), 2,76 (d, J = 17,94 Hz, 1H), 4,02 (d, J = 3,03 Hz, 2 H), 7,06 (dd, J = 8,08, 1,77 Hz, 1H), 7,20 (d, J = 1,77 Hz, 1H), 7,34 (d, J = 8,08 Hz, 1H), 7,69 (s, 1H), 8,44 (dd, J = 21,73, 2,02 Hz, 2 H).

Etapa 1: Éster etílico del ácido imidazo[1,2-b][1,2,4]triazina-6-carboxílico



Una solución de 3-amino-1,2,4-triazina (5,0 g,52 mmol) y bromopiruvato de etilo (11 ml, 88 mmol) en etanol (50 ml) se calentó a reflujo durante 20 minutos. La reacción se enfrió a temperatura ambiente y después se repartió entre 200 ml de EtOAc y 200 ml de agua. Las capas se separaron y la capa orgánica se secó sobre $MgSO_4$. Los sólidos se retiraron por filtración y después el disolvente se retiró por evaporación rotatoria. El residuo se purificó por cromatografía (90 g SiO2, EtOAc al 50%-70% en hexanos) para dar el producto deseado (181 mg, 1,8%). MS (ESI): 192,4 $(M+H)^+$.

Etapa 2: Imidazo[1,2-b][1,2,4]triazin-6-carbaldehído

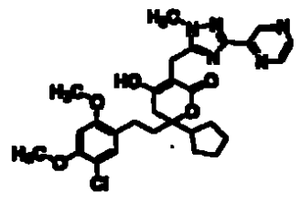


A una solución de éster etílico del ácido imidazo[1,2-b][1,2,4]triazina-6-carboxílico (500 mg, 2,6 mmol, de la etapa 1 anterior) en CH_2Cl_2 (15 ml) enfriada a -78°C se le añadió hidruro de diisobutilaluminio (2,6 ml, 1,5 M en tolueno). La reacción se agitó durante una hora y después se añadió una cantidad adicional de hidruro de diisobutilalumino (1 ml, 1,5 M). Después de 20 minutos más, la reacción fría se interrumpió con EtOAc (10 ml) y después con MeOH (10 ml). Después de que la reacción se hubiera calentado a temperatura ambiente, se añadieron 30 ml de HCl 0,3 M. Las capas se separaron. La capa acuosa se extrajo tres veces con 10 ml de CH_2Cl_2. Después, las capas orgánicas se combinaron y se secaron sobre $MgSO_4$ y los sólidos se retiraron por filtración. El líquido orgánico se concentró por evaporación rotatoria y el aceite resultante se cromatografió (40 g SiO_2,50 to 100% EtOAc en hexanos) para dar el producto deseado (47 mg, 12%). ^1H RMN (400 MHz, $CDCl_3$) δ 8,48 (s, 2 H), 8,62 (d,

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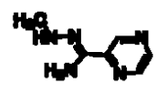
J = 1,77 Hz, 1H), 10,25 (s, 1H).

Ejemplo B(15): 6-[2-(5-cloro-2,4-dimetoxifenil)etil]-6-ciclopentil-4-hidroxi-3-[(1-metil-3-pirazin-2-il-1H-1,2,4-triazol-5-il)metil]-5,6-dihidro-2H-piran-2-ona



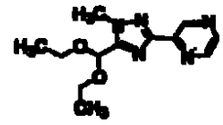
Una solución de 6-[2-(5-cloro-2,4-dimetoxi-fenil)-etil]-6-ciclopentil-dihidro-piran-2,4-diona (0,300 g, 0,78 mmol, de la etapa 6 mostrada a continuación) en isopropanol caliente (5 ml) se trató con $(CH_3)_2NHBH_3$ (48 mg, 0,815 mmol, 1,04 equiv) y después con una solución de hidrocloruro de 2-metil-5-pirazin-2-il-2H(1,2,4]triazol-3-carbaldehído monohidrato (229 mg, 0,819 mmol, 1,05 equiv, de la etapa 3 mostrada a continuación) en isopropanol (3 ml) que contenía trietilamina (0,230 ml, 2 equiv). La mezcla de reacción se agitó a temperatura ambiente produciendo una conversión completa en 1 h. La mezcla se acidificó con HCl acuoso 1 M a un valor de pH de 2, se agitó durante 10 min y se concentró *al vacío* para producir una resina. Ésta se diluyó con agua y se extrajo con diclorometano que contenía metanol al 10% (3 x 15 ml). El extracto se secó sobre Na_2SO_4, se filtró y se concentró, produciendo el producto bruto (410 mg). Este material se cristalizó de nuevo en cloruro de metileno/éter caliente, después el sólido resultante se trituró con acetona que contenía éter de petróleo, se filtró y se secó, produciendo el producto del título (107 mg, 24%). ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,26-1,75 (m, 8H), 1,78-2,13 (m, 2H), 2,37 (m, 1H), 2,45-2,50 (m, 2H, solapado con DMSO-d6), 2,65 (d, J = 17,9 Hz, 1H), 2,73 (d, J = 17,9 Hz, 1H), 3,73 (s, m solapado,5H), 3,80 (s, 3H), 3,95 (s, 3H), 6,63 (s, 1H), 7,05 (s, 1H), 8,6 (m, solapado, 2H), 8,93 (s, 1H), 11,07 (s a, 1H). LCMS (APCI) calculado para $C_{28}H_{32}ClN_5O_5$: 553,21, encontrado ($M+H^+$): 554,4 m/z.

Etapa 1: N'-metilpirazino-2-carbohidrazonamida



Un matraz de 2 litros se cargó con 2-cianopirazina fundida (50,0 g, 0,48 mol), metilhidrazina (80,0 g, 1,7 mol, 3,6 equiv) y etanol (300 ml). La mezcla se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 3 h, después de lo cual la reacción se mostró completa según el análisis por LC/MS. Las agujas amarillas que habían cristalizado se filtraron y se lavaron con heptano para retirar la metilhidrazina sin reaccionar. El filtrado se concentró *al vacío* hasta un bajo volumen, dando como resultado la formación de un precipitado adicional. Los procesos de filtración, lavado y concentración se repitieron tres veces, produciendo lotes adicionales de producto. Los lotes combinados se suspendieron en heptano (400 ml), se agitaron durante 1 h, se filtraron, se lavaron con heptano y se secaron *al vacío* a 50°C durante una noche, produciendo la amidrazona del título (55,4 g, 76%). ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,01 (s, 3H), 3,80 (s a, 1H),5,04 (s a, 2H), 8,41 (s, 1H), 8,48 (s, 1H), 9,32 (s, 1H). MS (APCI) calculado para $C_6H_9N_5$: 151,09, encontrado ($M+H^+$): 152,1

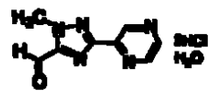
Etapa 2: 2-(5-Dietoximetil-1-metil-1H-[1,2,4]triazol-3-il)-pirazina



Un matraz de 1 litro se cargó con dietoxiacetonitrilo (25,0 g, 0,19 mol), una solución de metóxido sódico en metanol (4,32 g of una solución al 25 % en peso, 0,02 mol, 10% en moles) y metanol (200 ml). La mezcla se agitó a temperatura ambiente durante 20 h, produciendo una solución del éster imidato, éster metílico del ácido 2,2-dietoxiacetimídico. La mezcla de reacción se trató con la amidrazona, N metilpirazina-2-carbohidrazonamida (26,7 g, 0,19 mol, 1 equiv) de la etapa 1 y ácido acético (18,0 g, 0,30 mol, 1,5 equiv). La mezcla se agitó a temperatura ambiente durante 3 h, después de lo cual la reacción se había completado según mostró el análisis por LC/MS. Los volátiles se retiraron al vacío, produciendo un aceite viscoso. Éste se basificó con Na_2CO_3 al 20% (100 ml) y $NaHCO_3$ saturado (200 ml) y se extrajo varias veces con éter (2 l en total). La fase etérea se lavó con agua (1 x 200 ml), se secó sobre Na_2SO_4, se filtró y se evaporó, produciendo el acetal del título en forma de un aceite amarillo (44,6 g, 89%). ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,24 (t, J = 6 Hz, 6H), 3,62 (modelo de 5 líneas, J = 6 Hz, 2H), 3,79 (modelo de 5 líneas, J = 6 Hz, 2H), 4,08 (s, 3H),5,68 (s, 1H), 8,56 (m, 1H), 8,63 (m, 1H). 9,34 (s, 1H). MS (APCI) calculado para $C_{12}H_{17}N_5O_2$: 263,14, en-

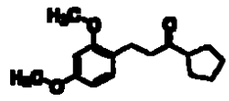
contrado ($M+H^+$): 264,1

Etapa 3: Dihidrocloruro de 2-metil-6-pirazin-2-il-2H-[1,2,4]triazol-3-carbaldehído *monohidrato*



El acetal de la etapa 2, 2-[5-(dietoximetil)-1-metil-1H-1,2,4-triazol-3-il]pirazina (44,5 g, 0,17 mol) se disolvió en agua (150 ml) y HCl concentrado (30,0 ml de 12 M, 0,36 mol, ~ 2 equiv). La solución se desgasificó con nitrógeno durante 2 min y se calentó en un baño de aceite a una temperatura de baño de 60°C durante 2 h, dando como resultado una hidrólisis completa del grupo acetal. Los volátiles se retiraron al vacío, produciendo un sólido amarillo (49,8 g). Éste se suspendió en diclorometano (1 l), se calentó a reflujo en una atmósfera de nitrógeno for 1 h y después se filtró mientras aún estaba caliente. La torta de filtro se lavó con diclorometano y se secó *al vacío* a 50°C durante 4 h, produciendo el producto del título (41,0 g, 81 %) en forma de un sólido amarillo higroscópico. ^{1}H RMN (300 MHz, DMSO-d_6): δ 4,21 (s, 3H), 8,50 (s a, 4H), 8,75 (m, 2H), 9,27 (s, 1H), 10,01 (s, 1H). MS (APCI) calculado para $C_8H_7N_5O$: 189,07, encontrado ($M+H^+$): 190,1, 208,1 (hidrato); Análisis calculado para $C_8H_{11}C1_2N_5O_2$: C, 34,30; H, 3,96; N, 25,00; 0, 11,42; Cl, 25,31, Encontrado: C, 33,43; H, 3,98; N, 24,70; 0, 11,17; Cl, 25,44,

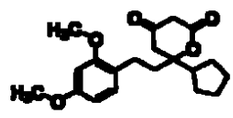
Etapa 4: 1-Ciclopentil-3-(2,4-dimetoxi-fenil)-propan-1-ona



Una solución de 2,4-dimetoxibenzaldehído (10,27 g, 45 mmol) y metil ciclopentil cetona (6,06 g,54 mmol) en etanol anhidro (81 ml) se trató con NaOH 5 M (ac) (18 ml, 90 mmol) y la mezcla se agitó a temperatura ambiente durante 18 h. Los volátiles se retiraron al vacío. El residuo se extrajo con éter (100 ml) y el extracto se lavó con agua (3 x 60 ml) y después con salmuera. La solución etérea se secó sobre $MgSO_4$, se filtró y se concentró al vacío, produciendo la chalcona intermedia con un rendimiento de 14,63 g. El intermedio bruto (14,52 g) se disolvió en 110 ml de acetato de etilo, se trató

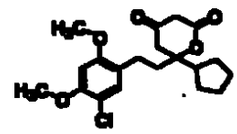
con óxido de platino (5% en moles) y se agitó en una atmósfera de H_2 a temperatura ambiente durante una noche. El Pt se filtró a través de un embudo fritado fino y el residuo negro se lavó con acetato de etilo. El filtrado se concentró *al vacío para dar una resina amarillenta*. La resina se cromatografió usando gel de sílice y 6:1 de hexanos/acetato de etilo, produciendo 6,02 g (41%) de la cetona en forma de un aceite incoloro. ^{1}H RMN ($CDCl_3$): δ 1,48-1,81 (m, 8H), 2,67 (m, 2H), 2,80 (m, 3H), 3,76 (s, 3H), 3,75 (s, 3H), 6,37 (dd, J = 8,1, 2,1Hz, 1H), 6,41 (d, J = 2,1Hz, 1H), 7,00 (d, J = 8,1Hz, 1H). MS(APCI) calculado para $C_{16}H_{22}O_3$: 262,2; encontrado ($M+H^+$): 263,1,

Etapa 5: 6-ciclopentil-6-[2-(2,4-dimetoxi-fenil)-etil-dihidro-piran-2,4-diona



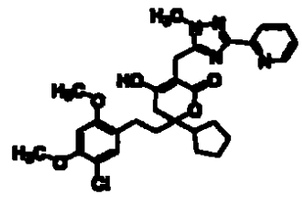
Se disolvió acetoacetato de metilo (1,63 ml, 15,1 mmol) en THF seco (42 ml) y se enfrió a 0°C. Se añadieron cuidadosamente NaH (60% en aceite mineral, 0,604 g, 15,1 mmol) y la mezcla de reacción se agitó durante 20 min. Se añadió gota a gota una solución de BuLi en hexanos (1,6 M, 9,44 ml, 15,1 mmol) y la mezcla resultante se agitó durante 20 minutos más. Se añadió gota a gota una solución de 3-(2,4-dimetoxifenil)-1ciclopentilpropan-1-ona (2,33 g, 7,55 mmol) de la etapa 4 anterior en THF (37 ml). Después de agitar durante 1 h, la mezcla de reacción se inactivó con NH_4Cl acuoso saturado (100 ml) y se extrajo con Et_2O (600 ml). La fase orgánica se secó sobre $MgSO_4$ y se evaporó. El residuo después se agitó durante una noche en una mezcla de NaOH 0,1 M (370 ml) y THF (37 ml). Después de la adición de una solución acuosa al 10% de $KHSO_4$ acuoso (50 ml), la mezcla resultante se agitó durante 30 min y después se extrajo con Et_2O (600 ml). La fase orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y se evaporó. El residuo se purificó por cromatografía en columna ultrarrápida (50% EtOAc en hexanos) para dar el producto (1,54 g,52%) en forma de una espuma blanca. ^{1}H RMN ($CDCl_3$) δ 1,43 (m, 2 H), 1,78 (m, 8 H), 2,33 (m, 1H), 2,58 (m, 2H), 2,78 (s, 2H), 3,43 (s, 2H), 3,78 (s, 6H), 6,37 (s, 1H), 6,47 (s, 1H), 6,93 (d, J = 7,93 Hz, 1H). MS (APCI) calculado para $C_{20}H_{26}O_5$: 346,2; encontrado (M+1): 347,0.

Etapa 6: 6-[2-(5-cloro-2,4-dimetoxi-fenil)-etil]-6-ciclopentil-dihidro-piran-2,4-diona



Una solución de 6-[2-(2,4-dimetoxifenil)etil]-6-ciclopentildihidro-2H-piran-2,4(3H)-diona (de la etapa 5, anterior) (4,50 g, 13 mmol) en CH_2Cl_2 (20 ml) se enfrió a -5°C y se trató gota a gota con una solución de SO_2Cl_2 (1,94 g, 14,3 mmol) en CH_2Cl_2 (10 ml) en una atmósfera de nitrógeno. La mezcla de reacción se agitó durante 15 minutos más a -5°C y después se dejó calentar gradualmente a temperatura ambiente. Después de un tiempo de reacción total de 2 h, se añadió una solución acuosa de $NaHCO_3$ (5 % en peso) para conseguir un pH de 8 en la fase acuosa. Los volátiles se retiraron al vacío. El residuo se trató con agua y se extrajo con acetato de etilo (3 x 25 ml). El extracto de acetato de etilo combinado se acidificó a pH 2 usando HCl 2 N y después se lavó con agua. La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró hasta dar un sólido amarillento. La recristalización en éter produjo el producto del título en forma de un sólido blanco (2,18 g, 44%). ^1H RMN ($CDCl_3$) δ 1,74 (m, 8H), 2,32 (m, 1H), 2,58 (m, 2H), 2,78 (s, 2H), 3,43 (s, 2H), 3,82 (s, 3H), 3,92 (s, 3H), 6,44 (s, 1H), 7,07 (s, 1H). HRMS calculado para $C_{20}H_{25}O_5Cl$ ($M+H^+$): 381,1469, encontrado 381,1475,

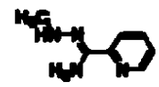
Ejemplo B(16): 6-[2-(5-cloro-2,4-dimetoxifenil)etil]-6-ciclopentil-4-hidroxi-3-[(1-metil-3-piridin-2-il-1H-1,2,4-triazol-5-il)metil]-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo B(15) usando 2-metil-5-piridin-2il-2H-[1,2,4]triazol-3-carbaldehído de la etapa 3 mostrada a continuación en lugar de dihidrocloruro de 2-metil-5-pirazin-2-il-2H[1,2,4]triazol-3-carbaldehído monohidrato y omitiendo la trietilamina. El material bruto obtenido después del tratamiento acuoso (425 mg) se cromatografió sobre gel de sílice usando un gradiente de acetato de etilo que contenía metanol al 1% a metanol al 15%. Las fracciones que contenían el producto se concentraron y el sólido resultante se recristalizó

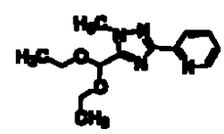
en diclorometano/éter caliente, produciendo 43 mg (10%) del producto del título en forma de la sal hidrocloruro hidratada. ^{1}H RMN (300,MHz, DMSO-d_6): δ 1,15-1,6 (m, 8H), 1,6-1,9 (m, 2H), 2,05 (m, 1H), 2,15-2,45 (m, 4H, solapado), 3,6- 3,75 (s, m solapado,5H), 3,80 (s, 3H), 3,95 (s, 3H), 6,67 (s, 1H), 6,92 (s, 1H), 7,3 (m a, 1H), 7,85 (m a, 2H), 8,92 (m a, 1H). LC*MS* (APCI) calculado para $C_{28}H_{33}ClN_4O_5$: 552,21, encontrado (M+H$^+$): 553,4 m/z. Análisis calculado para $C_{28}H_{34}Cl_2N_4O_5$: C,57,33; H,5,97; N, 9,22; Encontrado: C,57,46; H,5,41; N, 8,12,

Etapa 1: N'-metilpiridina-2-carbohidrazonamida



Este compuesto se preparó por una modificación del procedimiento informado en (J. *Het Chem.* **1975**, 12, 855): UN matraz de fondo redondo de 2 litros y de 3 bocas se cargo con 2-cianopiridina (40 g, 0,384 mol), metilhidrazina (93,7 g,5,3 equiv, 2,035 mol) y etanol (200 ml). La reacción se agitó en una atmósfera de N_2 durante una noche a temperatura ambiente. Se añadió un equivalente adicional de hidrazina (6,3 equiv *total acumulativo en la mezcla de reacción) y se agitó durante* 2-3 h *más a temperatura* ambiente. El EtOH y el exceso de hidrazina se retiraron por destilación *al vacío* para producir un sólido cristalino amarillo. El sólido amarillo se trituró con benceno, produciendo una suspensión de cristales blancos. Los cristales se filtraron, se lavaron con una cantidad mínima de benceno y se secaron durante una noche en una estufa de vacío a 50°C. La reacción produjo 41,33 g (71,6%) del producto en forma de cristales blancos. ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,97 (s, 3H), 4,02 (s a, 1H),5,30 (s a, 1H), 7,20 (m, 1H), 7,66 (m, 1H), 8,08 (m, 1H), 8,45 (m, 1H). MS (APCI) calculado para $C_7H_{10}N_4$: 150,09, encontrado (M+H$^+$): 151,3

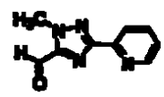
Etapa 2: 2-(5-Detoximetil-1-metil-1H-[1,2,4]triazol-3-il)-piridina



UN matraz de fondo redondo de 1 litro y de 3 bocas se cargó con una solución

preparada a partir de metóxido sódico (9,41 g, 0,174 mol, 0,9 equiv) en metanol anhidro (150 ml). A la solución del metóxido de le añadió lentamente durante 15 minutos mediante un embudo de adición una solución de dietoxiacetonitrilo (25 g, 0,193 mol) en metanol anhidro (70 ml). Después, la reacción se agitó durante una noche a temperatura ambiente y el exceso de metanol se evaporó al vacío. El aceite resultante se diluyó con agua y se extrajo en acetato de etilo (2 x 250 ml) y después en CH_2Cl_2 (2 x 250 ml). Las fases orgánicas se combinaron y se secaron sobre Na_2SO_4, se filtraron y se concentraron al vacío, produciendo 9 g, (29%) de 2,2-dietoxietanimidoato de metilo bruto que tenía una pureza de 80-85% según mostró el análisis de 1H RMN. Esto se usó en la siguiente etapa sin purificación adicional. Un matraz de fondo rédondo de 500 ml se cargó con una solución de la amidrazona de la etapa 1, N-metilpiridina-2-carbohidrazonamida (22 g, 0,0548 mol) en metanol (75 ml), junto con una solución del éster imidato bruto (8,84 g, 0,0548 mol) en metanol (75 ml). La mezcla se trató con ácido acético glacial (4,75 ml, 1,5 equiv) y se agitó a temperatura ambiente durante una noche mientras se controlaba por LC/MS para la desaparición de la amidrazona. El metanol se evaporó *al vacío y el aceite resultante se neutralizó con* $NaHCO_3$ acuoso saturado. El producto se extrajo en acetato de etilo (3 x 150 ml) y la fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró, para dar un aceite amarillo (11,06 g, rendimiento bruto de 76 %) del acetal intermedio, que se usó en la siguiente etapa sin purificación.

Etapa 3: 2-metil-5-piridin-2-il-2H-[1,2,4]triazol-3-carbaldehído

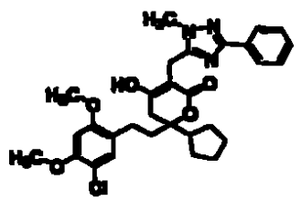


El acetal de la etapa 2, 2-[5-(dietoximetil)-1-metil-1H-1,2,4-triazol-3-il]piridina (11,06 g, 0,042 mol) se disolvió en 1,5 equiv de HCl (ac) 2 N y se agitó a 40-50°C durante una noche. La mezcla se concentró, produciendo un aceite viscoso que después se basificó a pH 10 usando Na_2CO_3 acuoso saturado. La mezcla después se extrajo usando acetato de etilo (4 x 200 ml). La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró, hasta dar un sólido amarillo. El sólido se disolvió en una cantidad mínima de acetato de etilo caliente, se raspó y se diluyó con hexanos hasta cristalizar el producto, produciendo 3,6 g (45 %) del aldehído deseado en forma de un polvo amarillo. ^1H RMN (300 MHz, $CDCl_3$): δ 4,28 (s, 3H), 7,46 (m, 1H), 7,82 (m, 1H), 8,15 (m, 1H),

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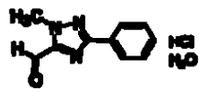
8,78 (m, 1H), 10,08 (s, 1H). MS (APCI) calculado para $C_9H_8N_4O$: 188,07, encontrado ($M+H^+$): 189,3.

Ejemplo B(17): 6-[2-(5-cloro-2,4-dimetoxifenil)etil]-3-ciclopentil-4-hidroxi-3-[(1-metil-3-fenil-1H-1,2,4-triazol-5-il)metil-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo B(15) usando hidrocloruro de 2-metil-5-fenil-2H[1,2,4]triazol-3-carbaldehído hidrato de la etapa 1 mostrada a continuación en lugar de dihidrocloruro de 2-metil-5-pirazin-2-il-2H-[1,2,4]triazol-3-carbaldehído monohidrato y usando un equivalente de trietilamina en lugar de dos. Rendimiento: 100 mg (23%). ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,30-1,77 (m, 8H), 1,88 (m. 1H), 2,1 (m, 1H), 2,35 (m, 1H), 2,45-2,55 (m, 2H, solapado con DMSO-d6), 2,68 (d, J = 17,6 Hz, 1H), 2,73 (d, J = 17,6 Hz, 1H), 3,65-3,7 (s, solapado con ABQ, J = 16,7 Hz, total 5H), 3,82 (s, 3H), 3,86 (s, 3H), 6,65 (s, 1H), 7,12 (s, 1H), 7,28 (m, 3H), 7,71 (d, J = 8 Hz, 2H), 10,98 (s a, 1H). LCMS (APCI) calculado para $C_{30}H_{34}ClN_3O_6$: 551,22, encontrado ($M+H^+$): 552,4 m/z.

Etapa 1: Hidrocloruro de 2-metil-5-fenil-2H-[1,2,4]triazol-3-carbaldehído hidrato

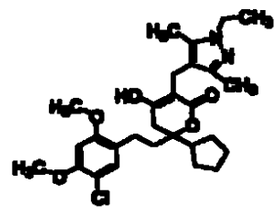


El compuesto del título se preparó de una forma análoga a la etapa 3 del ejemplo B(15) usando Nmetilbenceno-carbohidrazonamida (la base libre de la amidrazona informada en: Metz, H.J.; Neunhoeffer, H. *Chem. Ber.* **1982**, *115*, 2807) en lugar de N'-metilpirazina-2-carbohidrazonamida en la etapa 2 de ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 4,17 (s, 3H), 7,30 (m a, 3H), 7,48 (m, 3H), 8,02 (d, J = 9 Hz, 2H), 9,99 (s, 1H). MS (APCI) calculado para $C_{10}H_9N_3O$: 187,07, encontrado ($M+H^+$): 188,3.

Ejemplo B(18): 6-[2-(5-cloro-2,4-dimetoxifenil)etil]4-ciclopentil-3-[(1-etil-3,5dimetil-

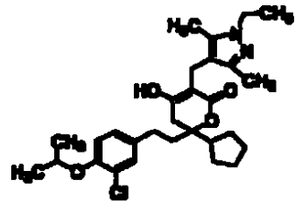
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1H-pirazol-4-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga a la del ejemplo B(15) usando 1-etil-3,5-dimetil1H-pirazol-4-carbaldehído en lugar de dihidrocloruro de 2-metil-5-pirazin-2-il-2H-(1,2,4]triazol-3-carbaldehído monohidrato y omitiendo la trietilamina. Después del tratamiento acuoso, el producto se recristalizó en una mezcla de acetato de etilo caliente, metanol y éter, produciendo 242 mg (60%) del producto del título. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,14 (t, J = 7 Hz, 3H), 1,23-1,8 (m, solapado, 10H), 2,01 (s, 3H), 2,10 (s, 3H), 2,23 (m, 1H), 2,38 (m, 2H), 2,5 (d, 1H, solapado con pico de DMSO-d6), 2,67 (d, J = 17,9 Hz, 1H), 3,15 (ABQ, J = 15,2 Hz, 2H), 3,74 (s, 3H), 3,82 (s, q solapado, total 5H), 6,7 (s, 1H), 7,0 (s, 1H), 10,58 (s a, 1H). LC-MS (APCI) calculado para $C_{28}H_{37}ClN_2O_6$: 516,24, encontrado (M+H$^+$): 517,4 m/z.

Ejemplo B(19): 6-[2-(3-cloro-4-isopropoxifenil)etil]-6-ciclopentil-3-[(1-etil-3,5-dimetil-1H-pirazol-4-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona

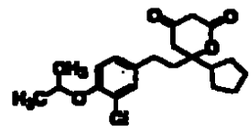


Una solución de 6-[2-(3-cloro-4-isopropoxi-fenil)-etil]-6-ciclopentil-dihidro-piran-2,4diona (379 mg; 1,0 mmol de la etapa 1 mostrada a continuación) y 1-etil-3,5-dimetil-1H-pirazol-4-carbaldehído (152 mg; 1,1 mmol) en metanol se calentó a 40°C durante una noche. La mezcla de reacción se trató con $(CH_3)_2NHBH_3$ (65 mg, 1,1 equiv) y se calentó de nuevo a 40°C durante una noche. La reacción se repartió entre EtOAc y H_2O. La capa de EtOAc se secó con Na_2SO_4, se concentró y se purificó por HPLC de fase inversa usando HOAc al 0,1% en H_2O y CH_3CN. (Columna: Water's Bondapak, C18, tamaño de partículas: 37-55 micrómetros, tamaño de la columna: 47x300 mm;

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605

Caudal: 70 ml/min; El detector se programó a 254 nm; Tampón A: HOAc al 0,1% en H_2O; Tampón B:HOAc al 0,1% en CH_3CN. La columna se equilibró en A durante 20 minutos. La muestra se disolvió en 5 ml de DMSO, se filtró y se inyectó en la columna. El gradiente se mantuvo a 75% de A/25% de B durante 5 minutos y después se incrementó a 55% de A/45% de B en 15 minutos y después se continuó de forma isocrática a 45% de B durante 25 minutos más. El producto deseado eluyó a los 28 minutos.) Las fracciones que contenían el producto se liofilizaron para producir el compuesto del título en forma de un polvo (196,2 mg, 40%). ^{1}H RMN (400 MHz, DMSO-d_6): δ 1,13 (t, 3H), 1,26 (d, m solapado, 8H), 1,35-1,63 (m, 6H), 1,75 (m, 2H), 2,02 (s, 3H), 2,10 (s, 3H), 2,21 (m, 1H), 2,39 (m, solapado, 3H), 2,61 (d, J = 16,4 Hz, 1H), 3,1 (m, 2H, solapado con pico de H_2O), 3,81 (q, 2H), 4,56 (modelo de 7 líneas, 1H), 6,90 (d, J = 8,8 Hz, 1H), 7,00 (d, J = 8,8 Hz, 1H), 7,11 (s, 1H). LC-MS (APCI) calculado para $C_{29}H_{39}ClN_2O_4$: 514,26, encontrado ($M+H^+$): 515,3 m/z.

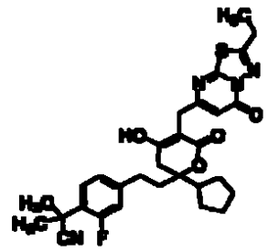
Etapa 1: 6-[2-(3-cloro-4-isopropoxi-fenil)-etil]-6-ciclopentil-dihidro-pirán-2,4-diona



El compuesto del título se preparó de una forma análoga al ejemplo B(2) sustituyendo 4-bromo-2-cloro-1-isopropoxi-benceno en lugar de 4-bromo-2-cloro-1-metanosulfonil-benceno en la etapa 2 de ese ejemplo. ^{1}H RMN ($CDCl_3$): δ 1,36 (d, J = 6,0 Hz, 6H), 1,52-1,82 (m a, 8H), 1,94 (m, 2H), 2,27 (m, 1H), 2,60 (t, J = 7,9 Hz, 2H), 2,76 (s, 2H), 3,43 (s, 2H), 4,50 (m, 1H), 6,86 (d, J = 8,5 Hz, 1H), 6,94 (d, J = 8,5 Hz, 1H), 7,14 (s, 1H) (m, 3H). Análisis calculado para $C_{21}H_{27}ClO_4$: C, 66,57; H, 7,18. Encontrado: C, 66,33; H, 6,96.

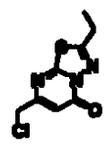
Ejemplo B(20): 2-[4-(2-{2-ciclopentil-5-[(2-etil-5-oxo-5H-[1,3,4]tiadiazolo[3,2-a]pirimidin-7-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-pirán-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo

607
606



El compuesto del título se preparó en una escala de 0,5 mmol de forma análoga al ejemplo B(19) con la excepción de que se usó 2-{4-[2-(2-ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]-2-fluoro-fenil}-2-metilpropionitrilo de la etapa 3 del ejemplo A(84) en lugar de 6-[2-(3-cloro-4-isopropoxi-fenil)-etil]-6-ciclopentil-dihidro-piran-2,4-diona y 2-etil-5-oxo-5H-[1,3,4]tiadiazolo[3,2-a]pirimidina-7carbaldehído de la etapa 2 mostrada a continuación en lugar de 1-etil-3,5-dimetil-1H-pirazol-4-carbaldehído. Rendimiento: 10 mg (4%). ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,29 (t, 3H), 1,35-1,7 (s, m solapado, 14H), 1,99 (m, 2H), 2,38 (m, 1H), 2,63 (m, solapado, 3H), 2,75 (d, 1H), 3,03 (q, 2H), 3,48 (ABq, 2H), 6,06 (s, 1H), 7,10 (m, solapado, 2H), 7,35 (m, 1H), 10,98 (s, 1H). LC-MS (APCI) calculado para $C_{30}H_{33}FN_2O_4S$: 564,22, encontrado ($M+H^+$): 565,2 m/z.

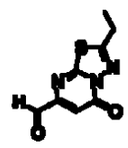
Etapa 1: 7-Clorometil-2-etil-[1,3,4]tiadiazolo[3,2-a]pirimidin-5-ona



El compuesto del título e preparó por una modificación de un procedimiento descrito en: (J. *Heterocyclic Chem.* **1983**, 20, 1053). Un matraz de litros y de 3 bocas con agitación en la parte superior se cargó con ácido polifosfórico caliente (aprox 250 g), 2-amino-5-etil-1,2,4-tiadiazol (45,2 g, 0,35 mol) y 4-cloroacetoacetato de etilo (86,4 g, 0,525 mol, 1,5 equiv). La mezcla se calentó a 110°C con agitación vigorosa. Después de 30 minutos, tuvo lugar una reacción exotérmica, dando como resultado un incremento en la temperatura de 140°C, un incremento en la viscosidad y la aparición de un color más oscuro. El calentamiento se detuvo, la mezcla de reacción se enfrió a 80°C y después se trató lentamente con agua (300 ml) mediante un embudo de adición. La mezcla resultante se transfirió a un vaso de precipitados de 3 litros, se enfrió en un baño de hielo y se neutralizó a pH 6-7 usando NaOH acuoso (10%). El sólido precipitado se filtró, se lavó con agua, éter y y éter de petróleo y después se secó al

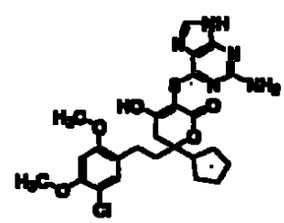
vacío, produciendo 66,4 g (83%) del producto del título en forma de un sólido cristalino de color arena. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,46 (t, J = 7,5 Hz, 3H), 3,09 (q, J = 7,5 Hz, 2H), 4,42 (s, 2H), 6,61 (s, 1H). MS (APCI) calculado para $C_8H_8ClN_3OS$: 229,01, encontrado ($M+H^+$): 230,0,

Etapa 2: 2-Etil-5-oxo-5H-[1,3,4]tiadiazolo[3,2-a]pirimidina-7-carbaldehído



Una mezcla de 7-clorometil-2-etil-[1,3,4]tiadiazolo[3,2-a]pirimidin-5-ona (11,48 g,50 mmol), yoduro sódico (15 g, 100 mmol, 2 equiv), bicarbonato sódico (12,6 9, 150 mmol, 3 equiv), agua (25 ml) y DMSO (250 ml) se agitó y se calentó a 80°C durante 18 horas. La mayor parte de los volátiles se retiró en el evaporador rotatorio y después el residuo se trató con acetato de etilo para precipitar la sal y la mezcla se filtró. El filtrado se liofilizó y se cromatografió sobre gel de sílice usando un gradiente de acetato de etilo a metanol al 3% en acetato de etilo, produciendo 2-etil-7-hidroximetil-[1,3,4]tiadiazolo[3,2-a]pirimidin-5-ona (4,24 g, 40%). Este alcohol se disolvió en acetona (150 ml) y se calentó a reflujo durante 3 días con un total de 15 equivalentes de MnO_2 y durante este tiempo se añadieron porciones de 3 equivalente, produciendo la completa conversión en el aldehído correspondiente. La mezcla de reacción se filtró a través de celite, la torta se lavó con acetona (3 x 100 ml) y el filtrado se concentró *in vacuo*, produciendo el producto del título (2,84 g, 67%). ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,55 (t, 3H), 3,10 (q, 2H), 6,98 (s, 1H), 9,90 (s, 1H). MS (APCI) calculado para $C_8H_7ClN_3O_2S$: 209,03, encontrado ($M+H^+$): 210,2.

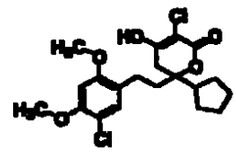
Ejemplo B(21): 3-[(2-Amino-7H-purin-6-il)tio]-6-[2-(5-cloro-2,4-dimetoxi-fenil)etil]-6-ciclopentildihidro-2H-piran-2,4(3H)-diona



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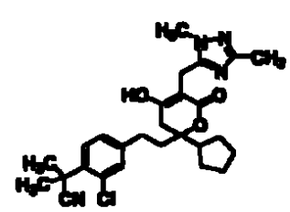
Una mezcla de 3-cloro-6-[2-(5-cloro-2,4-dimetoxi-fenil)-etil]-6-ciclopentil-4-hidroxi-5,6-dihidro-piran-2-ona (190 mg, 0,46 mmol, de la etapa 1 mostrada a continuación), 2-amino-9H-purine-6-tiol (90 mg, 0,5 mmol) y trietilamina (1 equiv) en DMF (3 ml) se calentó a 50°C durante una noche. La mezcla de reacción se repartió entre agua y acetato de etilo. La fase orgánica se concentró y el producto se aisló HPLC de fase inversa, produciendo 38 mg (14%). ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,35-1,75 (m, 8H), 2,0 (m, 1H), 2,18 (m, 1H), 2,35-2,55 (m, 3H, solapado con DMSO-d6), 2,73 (d, J = 17,3 Hz, 1H), 2,83 (d, J = 17,3 Hz, 1H), 3,77 (s, 3H), 3,85 (s, 3H),5,75 (a a, 2H), 6,71 (s, 1H), 7,15 (s, 1H), 7,81 (s, 1H); LC-MS (APCI) calculado para $C_{25}H_{28}ClN_5O_6S$: 545,15, encontrado (M+H$^+$): 546,1 m/z.

Etapa 1: 3-Cloro-6-[2-(5-cloro-2,4-dimetoxi-fenil)-etil]-6-ciclopentil-4-hidroxi-5,6-dihidro-piran-2-ona



El compuesto del título se preparó por cloración de 6-[2-(5-cloro-2,4-dimetoxi-fenil)etil]-6-ciclopentil-dihidro-piran-2,4-diona de la etapa 6 del ejemplo B(15) con cloruro de sulfurilo en diclorometano a temperatura ambiente. ^{1}H RMN ($CDCl_3$) δ 1,51 (m, 8H), 1,79 (m, 1H), 2,06, (m, 2H), 2,45 (m, 2H), 2,60 (m, 1H), 2,67 (d, J = 17,75, 1H), 2,92 (d, J = 17,75, 1H), 3,82 (s, 3H), 3,92 (s, 3H), 6,44 (s, 1H), 7,06 (s, 1H). HRMS calculado para $C_{20}H_{24}O_5Cl_2$ (M+H$^+$) 415,1079, encontrado 415,1083.

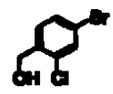
Ejemplo B(22): 2-[2-Cloro-4-(2-(2-ciclopentil-5-[(1,3-dimetil-1H-1,2,4-triazol-5-il)metil-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)fenil]-2-metilpropanonitrilo



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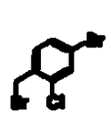
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 2-(2-cloro-4-[2-(2-ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]-fenil)-2-metil-propionitrilo.de la etapa 5 mostrada a continuación, en lugar de 6-[2-(3-cloro-5-etil-4-metoxi-fenil)-etil]-6-ciclopentil-dihidropiran-2,4-diona y 2,5-dimetil-2H-[1,2,4]triazol-3-carbaldehído en lugar de 5,7dimetil-[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído en ese ejemplo. ^{1}H RMN (300 MHz, DMSOd_6): δ 1,47-1,74 (m, 8 H), 1,79 (s, 6 H), 2,01-2,11 (m, 8 H), 2,36-2,42 (m, 1H), 2,56 (d, J = 16 Hz, 1H), 2,60-2,66 (m, 2 H), 2,77 (d, J = 16 Hz, 1H), 3,53 (d, J = 16 Hz, 1H), 3,62 (d, J = 16 Hz, 1H), 7,25 (dd, J = 8,2, 1,8 Hz, 1H), 7,4 (d, J = 1,8 Hz, 1H), 7,45 (d, J = 8,2 Hz, 1H). Análisis calculado para $C_{27}H_{33}ClN_4O_3$·0,25 H_2O: C, 64,66; H, 6,73; N, 11,17. Encontrado: C, 64,88; H, 6,74; N, 10,86. ESIMS (MH^+): 498.

Etapa 1: (4-Bromo-2-cloro-fenil)-metanol



Se disolvió ácido 4-bromo-2-clorobenzoico (5 g, 21,23 mmol) en THF seco (100 ml) y se enfrió a 0°C. Se añadió lentamente una solución 1 M de BH_3.THF en THF (31,85 ml, 31,85 mmol). La reacción se agitó durante una noche dejando que alcanzara lentamente la temperatura ambiente. Se añadieron K_2CO_3 sólido (19) y H_2O (100 ml) y la reacción se agitó durante 30 minutos. El THF se evaporó y el residuo se extrajo con EtOAc (30 ml). La fase orgánica se lavó con HCl 1 N (3 x 50 ml) y salmuera (3 x 50 ml), se secó sobre Na_2SO_4 y se evaporó. El residuo se purificó por cromatografía en columna ultrarrápida (EtOAc al 30% en hexanos) para dar el producto (2,80 g,50%) en forma de un aceite incoloro. ^{1}H RMN (400 MHz, $CDCl_3$): δ 4,73 (d, J = 5,8 Hz, 2H), 7,37 (d, J = 8,1Hz, 1H), 7,42 (dd, J = 8,1Hz, 1,7), 7,52 (d, J = 1,7 Hz, 1H).

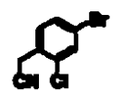
Etapa 2: 4-Bromo-1-bromometil-2-cloro-benceno



A una solución agitada magnéticamente de (4-bromo-2-cloro-fenil)-metanol (2,808, 12,67 mmol) de la etapa 1 anterior en CH_2Cl_2 (60,0 ml) en una atmósfera de

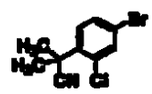
argón a 0°C, se le añadió tetrabromuro de carbono (4,41 g, 13,30 mmol) seguido de trifenilfosfina (3,48 g, 13,30 mmol). La mezcla resultante se agitó durante 4 horas a temperatura ambiente. La mezcla de reacción resultante se concentró al vacío y el residuo bruto se purificó por cromatografía en columna ultrarrápida (EtOAc al 10% en hexanos) para producir el bromuro intermedio en forma de un aceite transparente (3,59 g, 100%). ^{1}H RMN (400MHz, $CDCl_3$): δ 4,53 (s, 2H), 7,29 (d, J = 8,2 Hz, 1H), 7,39 (dd, J = 8,2, 1,9 Hz, 1H), 7,56 (d, J = 1,9 Hz, 1H).

Etapa 3: (4-Bromo-2-cloro-fenil)-acetonitrilo



A una solución agitada magnéticamente de 4-bromo-1-bromometil-2-cloro-benceno (3,59 g, 12,67 mmol) de la etapa 2 anterior y bromuro de tetrabutilamonio (0,419, 1,27 mmol) en CH_2Cl_2/H_2O 1:1 (60,0 ml), se le añadió una solución de KCN (2,48g, 38,01 mmol) en H_2O (30 ml). La mezcla naranja resultante se agitó a temperatura ambiente durante 3 horas. Las capas de la mezcla de reacción resultante se separaron y la capa orgánica se lavó con una solución saturada de $NaHCO_3$ (3 x 50 ml), después se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El residuo bruto se purificó por cromatografía ultrarrápida (EtOAc al 30% en hexanos) para producir el intermedio en forma de un aceite transparente (3,59 g, 100%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 3,79 (s, 2H), 7,37-7,60 (m, 3H).

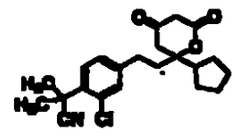
Etapa 4: 2-(4-Bromo-2-cloro-fenil)-2-metil-propionitrilo



Se suspendió NaH (95%, 1,18 g, 49,35 mmol) en DMF (25 ml) y se enfrió a 0°C. Se disolvió 4-bromo-2-cloro-fenil)-acetonitrilo (2,27 g, 9,87 mmol) de la etapa 3 anterior en THF (10 ml) y se añadió lentamente mediante una cánula y la mezcla de reacción se agitó durante 20 min. Se añadió MeI (6,10 ml, 98 mmol) y la mezcla resultante se agitó durante una noche a temperatura ambiente. La reacción se interrumpió con H_2O (50 ml). Los disolventes se retiraron al vacío y el residuo se repartió entre EtOAc y HCl 1 N

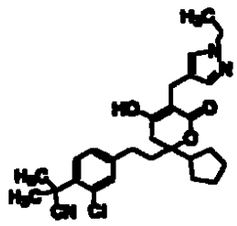
(50 ml). La fase orgánica se secó sobre Na_2SO_4 y se evaporó. El producto orgánico bruto se purificó por cromatografía en columna ultrarrápida (EtOAc al 5% en hexanos) para dar el producto (2,23 g, 87%) en forma de un aceite transparente. ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,34 (d, J = 8,4 Hz, 1H), 7,43 (dd, J = 8,4, 2,0 Hz, 1H), 7,61 (d, J = 1,8 Hz, 1H).

Etapa 5: 2-(2-Cloro-4-[2-(2-ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]-fenil)-2-metil-propionitrilo



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 2-(4-bromo-2-clorofenil)-2-metil-propionitrilo de la etapa 4 anterior en lugar de 1-benciloxi-2-etil-4yodo-5-propoxi-benceno en la etapa 4 de ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,39-1,71 (m, 8H), 1,81-1,87 (m, 8H), 2,10-2,15 (m, 1H), 2,59-2,68 (m, 2H), 3,51 (s, 2H), 3,75 (s, 2H), 7,11 (dd, J = 8,1Hz, 1,8), 7,27 (d, J = 1,8 Hz, 1H), 7,37 (d, J = 8,1Hz, 1H). MS (ESI): 388 $(M+H)^+$.

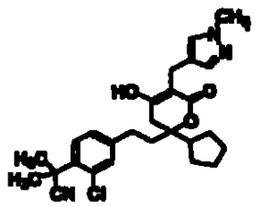
Ejemplo B(23): 2-[2-Cloro-4-(2-{2-ciclopentil-5-[(1-etil-1H-pirazol-4-il)metil]-4-hidroxi-6-oxo 3,6-dihidro-2H-piran-2 il}etil)fenil]-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo B(22) sustituyendo 1-etil-1H-pirazol-4-carbaldehído en lugar de 2,5-dimetil-2H-[1,2,4]triazol-3-carbaldehído en ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,43 (t, J = 7,2 Hz, 3 H), 1,4-1,76 (m, 8 H), 1,78 (s, 6 H), 2,04-2,28 (m, 4 H), 2,63-2,65 (m, 2 H), 3,64-3,74 (m, 3H), 4,06-4,08 (m, 2 H), 6,91-7,6 (m,5 H), 9,90 (s, 1H). Análisis calculado para $C_{28}H_{34}ClN_3O_3 \cdot 0{,}25\ H_2O$: C, 67,19; H, 6,95; N, 8,39, Encontrado: C, 67,30; H, 6,99; N,

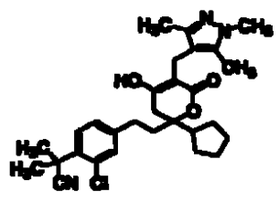
8,50. ESIMS (MH+): 497,

Ejemplo B(24): 2-[2-cloro-4-(2-(2-ciclopentil-4-hidroxi-5-[(1-metil-1H-pirazol-4-il)metil]-6-oxo-3,6-dihidro-2H-piran-2-il}etil)fenil]-2-metilpropanonitrilo



El compuesto del título se preparó de forma análoga al ejemplo B(22) sustituyendo 1-metil-1Hpirazol-4-carbaldehído en lugar de 2,5-dimetil-2H-[1,2,4]triazol-3-carbaldehído en ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,42-1,68 (m, 8 H), 1,85 (s, 6 H), 2,29-2,79 (m,5 H), 3,24-3,48 (m, 3 H), 3,61 (s, 2 H), 3,82 (s, 2 H), 6,89-7,39 (m,5 H), 7,33-7,45 (m, 1H). *Análisis calculado para* $C_{27}H_{32}ClN_3O_3 \cdot 0,5\ H_2O$: C, 66,04; H, 6,77; N, 8,56, Encontrado: C, 65,94; H, 6,73; N, 8,46. ESIMS (MH+): 483.

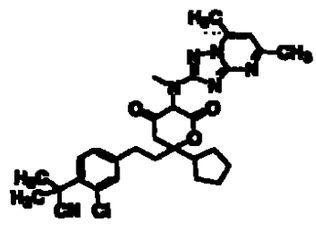
Ejemplo B(25): 2-(2-cloro-4-(2-(2-ciclopentil-4-hidroxi-6-oxo-5-((1,3,5-trimetil-1H-pirazol-4il)metil]-3,6-dihidro-2H-piran-2-il)etil)fenil]-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo B(22) sustituyendo 1,3,5-trimetil-1Hpirazol-4-carbaldehído en lugar de 2,5-dimetil-2H-[1,2,4]triazol-3-carbaldehído en ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,40-1,67 (m, 8 H), 1,75 (s, 6 H), 1,70-1,83 (m, 2 H), 1,99 (s, 3 H), 2,08 (s, 3 H), 2,21-2,25 (m, 1H), 2,49-2,52 (m, 3 H), 2,64 (d, J = 16 Hz, 1H), 3,08 (d, J = 14 Hz, 1H), 3,20 (d, J = 14 Hz, 1H), 3,50 (s, 3 H), 7,05 (dd, J = 8,2, 1,8 Hz, 1H), 7,27 (d, J = 1,8 Hz, 1H), 7,39 (d, J =8,2 Hz 1H), 10,7 (s, 1H). *Análisis calculado para* $C_{28}H_{36}ClN_3O_3.0,25\ H_2O$: C, 67,69; H, 7,15; N, 8,17, Encontrado: C, 67,72; H, 7,11; N, 8,02. ESIMS (MH+): 511.

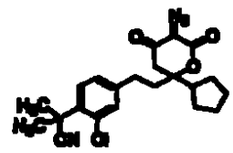
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Ejemplo B(26): 2-[2-cloro-4-(2-{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2il)(metil)amino]-4,6-dioxotetrahidro-2H-piran-2-il}etil)fenil]-2-metilpropanonitrilo



A una suspensión agitada 2-{2-cloro-4-[2-(2-ciclopentil-5-imino-4,6-dioxo-tetrahidro-piran-2-il)etil]-fenil}-2-metil-propionitrilo (0,83g, 1,53 mmol, de la etapa 1 mostrada a continuación), N-metil-4H-1,2,4-triazol-3,5-diamina (0,278, 1,53 mmol, de la etapa 3 mostrada a continuación) y $Rh_2(OAC)_2$ (0,00041g, 0,00092 mmol), en hexafluorobenceno (7 ml) en una atmósfera de argón se calentó a 80°C for 8 horas. La reacción se vertió en agua (10 ml) y se extrajo con EtOAc (3 x 5 ml). Las capas orgánicas se combinaron, se lavaron con NaCl saturado y se secaron sobre Na_2SO_4. Los disolventes se retiraron y el residuo se purificó por cromatografía en columna ultrarrápida (EtOAc al 30%-80% en hexanos y después MeOH al 2-4%/CH_2Cl_2) para dar el producto en forma de un sólido amarillo (0,086 g, 6%). ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,37-2,01 (m, 16 H), 2,26-2,33 (m, 1H), 2,41-2,69 (m, 8H), 3,32 (s, 2H), 3,43 (d, J = 2,5 Hz, 3 H),5,26-5,39 (m, 1H), 7,20-7,21 (m, 1H), 7,29-7,32 (m, 1H), 7,42-7,47 (m, 2H). ESIMS (MH+): 563.

Etapa 1: 2-{2-cloro-4-[2-(2-ciclopentil-5-imino-4,6-dioxo-tetrahidro-piran-2-il)-etil]-fenil}-2-metil-propionitrilo



A una solución agitada de 2-{2-cloro-4-[2-(2-ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]fenil}-2-metil-propionitrilo (0,5 g, 1,29 mmol) de la etapa 5 del ejemplo B(22) y pacetamidobencenosulfonil azida (0,46 g, 1,94 mmol) en THF (4 ml) en una atmósfera de argón se le añadió TEA (0,54 ml, 3,87 mmol). La solución resultante se

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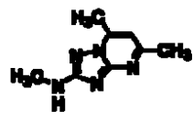
agitó a 25°C una noche. Los disolventes se retiraron y el residuo se purificó por cromatografía en columna ultrarrápida (EtOAc al 25%-60% en hexanos) para dar el producto en forma de un aceite amarillo. ESIMS (MH+): 414.

Etapa 2: N-metil-4H-1,2,4-triazol-3,5-diamina



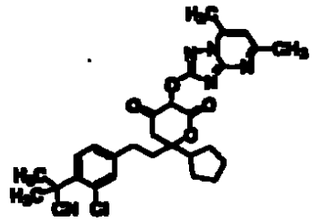
Una mezcla de N-ciano-N',S-dimetilisotiourea (100 g, 0,77 mol) y hidrazina hidrato al 85% (91,2 g, 1,55 mol) en EtOH (380 ml) se calentó a reflujo durante 2 horas. Durante la reacción se liberó metanotiol. Una vez que la reacción se había completado (controlada por TLC: CH_2Cl_2 / MeOH = 20/1), la mezcla de reacción se evaporó a sequedad. Se añadió éter de petróleo y el sólido se filtró y se lavó con éter de petróleo para dar el producto en forma de un sólido rosa (77 g, 88%). ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,59 (s, 3 H), 4,52-6,20 (m a, 3 H), 10,67 (s, 1H).

Etapa 3: N-metil-4H-1,2,4-triazol-3,5-diamina



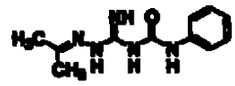
A una solución de N-metil-4H-1,2,4-triazol-3,5-diamina (75 g, 0,66 mol, de la etapa 2) en ácido acético glacial (375 ml) sed le añadió pentano 2,4-diona (66 g, 0,66 mol) y la mezcla se calentó a reflujo durante 8 horas. La mezcla de reacción se concentró a presión reducida. El residuo se recogió en CH_2Cl_2 (1000 ml). La solución se lavó con hidróxido sódico acuoso diluido y agua. Las capas acuosas combinadas se extrajeron con CH_2Cl_2 (1000 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4. La retirada de CH_2Cl_2 a presión reducida produjo un precipitado amarillo que se filtró y se lavó con éter de petróleo para dar el producto (64 g,55 %). ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,43 (s, 3 H), 2,56 (s, 3 H), 2,80 (s, 3 H), 6,64 (s, 1H), 6,80 (s, 1H).

Ejemplo B(27): 2-[2-cloro-4-(2(2-ciclopentil-5-[(5,7,dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)oxi]-4,6-dioxotetrahidro-2H-piran-2-il)etil)fenil]-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo B(26) sustituyendo 5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ol de la etapa 3 mostrada a continuación en lugar de (5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)-metil-amina en ese ejemplo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,61-1,84 (m, 10 H), 1,88 9s, 6H), 2,12-2,18 (m, 1H), 2,41-2,78 (m, 8H), 3,43 (s, 2H), 3,25-5,30 (m, 1H), 6,53-6,54 (m, 1H), 7,4-7,54 (m, 1H), 7,55-7,57 (m, 1H), 7,63 (s, 1H). ESIMS (MH+): 551.

Etapa 1: N-(Anilinocarbonil)-2-(1-metiletilideno)hidrazinacarboximidamida



A una suspensión of sodio (19 g, 0,82 mol) en acetona (1000 ml) se le añadió en porciones hidrocloruro de aminoguanidina (100 g, 0,91 mol). La mezcla se calentó a reflujo durante 60 minutos. El baño de calentamiento se retiró y se añadió gota a gota isocianato de fenilo (78,4 g, 0,65 mol) durante 30 minutos. La mezcla se calentó a reflujo durante 30 minutos más. La mezcla se vertió en agua enfriada con hielo (2,5 l). El aceite solidificó a temperatura ambiente y se agitó a temperatura ambiente durante una noche. El sólido se filtró y se lavó con éter de petróleo para producir el producto en forma de un sólido amarillo (150 g, 70 %).

Etapa 2: 5-Amino-2,4-dihidro-3H-1,2,4-triazol-3-ona

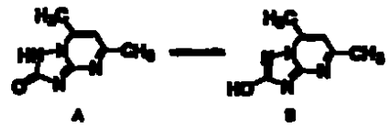


Una solución de N-(anilinocarbonil)-2-(1-metiletilideno)hidrazinacarboximidamida (150 g, 0,64 mol) en ácido clorhídrico (200 ml) se calentó a reflujo

~~677~~ 676

durante 30 minutos. La solución se llevó a pH = 9 con hidróxido sódico acuoso 1 N. La mezcla se concentró hasta que se formó un precipitado. La mezcla resultante se enfrió a temperatura ambiente y se mantuvo en el frigorífico durante una noche. El precipitado se filtró para dar el producto (29 g, 45%).

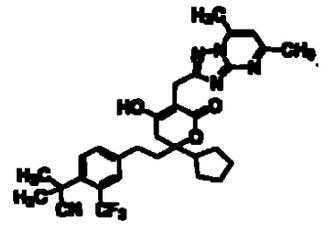
Etapa 3: 5,7-Dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ol



A B

A una solución de 5-amino-2,4-dihidro-3H-1,2,4-triazol-3-ona (29 g, 0,29 mol) en ácido acético glacial (140 ml) se le añadió pentano-2,4-diona (29 g, 0,29 mol) y la solución se calentó a reflujo durante 8 horas. La mezcla de reacción se concentró a presión reducida para producir un sólido amarillo. El sólido se filtró y se lavó con etanol (200 ml) para dar el producto (42 g, 80%).

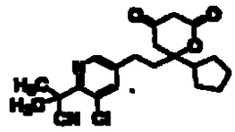
Ejemplo B(28): 2-[4-(2-(2-Ciclopentil-6-[(5,7-dimetil[1,2,4]triazolo[1,5]pirimidin-2-il)metil]4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-(trifluorometil)-fenil]-2--metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 2-[4-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]-2-(trifluorometil)fenil]-2-metilpropanonitrilo (ejemplo A(141)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]dihidro-piran-2,4-diona en ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,44-1,76 (m a, 8 H), 1,87 (s, 6 H), 2,23 (m, 2 H), 2,48-2,61 (m, 8,H), 2,80 (m, 3 H), 3,76 (d, J = 16,2 Hz, 1H), 3,89 (d, J = 16,2 Hz, 1H), 7,10 (s, 1H), 7,72 (s, 1H), 7,77 (m, 2 H), 11,01 (s, 1H). MS (ESI): 582,20 $(M+H)^+$

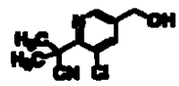
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Ejemplo B(29): 2-(3-Cloro-5-[2-(2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2 il)etil]piridin-2il)-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo B(2) sustituyendo 2-[3-cloro-5-(3ciclopentil-3-oxo-propil)-piridin-2-il]-2-metil-propionitrilo, de la etapa 7 mostrada a continuación, en lugar de 3-(3-cloro-4-metanosulfonil-fenil)-1-ciclopentil-propan-1-ona de ese ejemplo. ^{1}H RMN ($CDCl_3$) δ: 1,43-1,79 (m, 8 H), 1,84 (s, 6 H), 1,93-1,98 (m, 2 H), 2,25-2,30 (m, 1H), 2,69-2,84 (m, 4 H), 3,39-3,59 (m, 2 H), 7,55 (s, 1H), 8,29 (s, 1H).

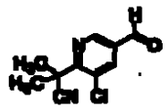
Etapa 1: 2-(3-cloro-5-hidroximetil-piridin-2-il)-2-metil-propionitrilo



A una solución agitada magnéticamente de ácido 5,6 dicloronicotínico (2,7 g, 14,06 mmol) en THF (70,0 ml) se le añadió isobutironitrilo (6,37 ml, 69,66 mmol) seguido de hexametildisilazida potásica 0,5 M en tolueno (70 ml). La mezcla naranja resultante se agitó a 60°C una noche. Los disolventes se retiraron y el residuo se repartió entre acetato de etilo (100 ml) y en HCl (100 ml). Las capas de la mezcla de reacción resultante se separaron y la capa acuosa se extrajo tres veces más con acetato de etilo. Las capas orgánicas *se combinaron y se secaron* sobre Na_2SO_4, se filtraron y se concentraron al vacío hasta dar un sólido amarillo (3,34 g). Este residuo bruto se disolvió en THF (80 ml) y la reacción se enfrió a 0°C. Se añadió una solución 1 M de BH_3.THF en THF (22,30 ml) y la reacción se agitó a 0°C durante 4 horas y después a temperatura ambiente durante una noche. Se añadieron K_2CO_3 sólido (2 g) y agua (100 ml) y la capa acuosa se extrajo tres veces más con acetato de etilo. Los extractos orgánicos se secaron sobre Na_2SO_4, se filtraron y se concentraron al vacío hasta dar un aceite transparente que se purificó por cromatografía en gel de sílice (hexanos) para dar el compuesto del título en forma de un sólido blanco (0,958, 32%). ESIMS (MH+): 210.

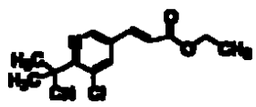
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Etapa 2: 2-(3-Cloro-5-formil-piridin-2-il)-2-metil-propionitrilo



Una solución de cloruro de oxalilo (0,45 ml,5,21 mmol) en CH_2Cl_2 seco (11 ml) se enfrió a -50°C. Se añadió gota a gota dimetil sulfóxido (0,76 g, 10,87 mmol) a una velocidad rápida. Después de 5 minutos, se añadió mediante una cánula 2-(3-cloro-5-hidroximetil-piridin-2-il)-2-metil-propionitrilo (0,95 g, 4,53 mmol) de la etapa 1 anterior, en CH_2Cl_2 seco (5 ml), seguido de trietilamina (3,16 g, 22,65 mmol). La reacción se agitó a -50°C durante 30 minutos más y después se dejó que alcanzara la temperatura ambiente. La reacción se vertió en agua (150 ml) y se extrajo con EtOAc (2 X 50 ml). Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo se purificó por cromatografía en columna ultrarrápida (EtOAc al 0-20% en hexanos) para dar el producto (0,58 g, 62% de rendimiento) en forma de un aceite transparente. ^1H RMN (400 MHz, $CDCl_3$): δ 1,90 (s, 6 H), 8,20 (s, 1H), 8,93 (s, 1H), 10,12 (s, 1H). ESIMS (MH+): 209.

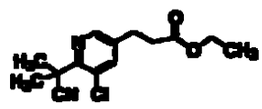
Etapa 3: Éster etílico del ácido 3-[5-cloro-4-(ciano-dimetil-metil)-piridin-3-il]-acrílico



Una solución de 2-(3-cloro-5-formil-piridin-2-il)-2-metil-propionitrilo (0,58 g, 2,78 mmol) de la etapa 3 anterior y (carbetoximetileno)trifenilfosforano (1,26 g, 3,61 mmol) en THF seco (12 ml) se calentó a 55°C y se mantuvo a esta temperatura durante una noche. Los disolventes se retiraron y el residuo se purificó por cromatografía en columna ultrarrápida (EtOAc al 0-20% en hexanos) para dar el producto (0,74 g, 96% de rendimiento) en forma de un sólido blanco. ^1H RMN (400 MHz, $CDCl_3$): 5 1,35 (t, J = 7,7 Hz, 3 H), 1,87 (s, 6 H), 4,29 (q, J = 14, 7,7 Hz, 2 H), 6,53 (d, J _ 16 Hz, 1H), 7,65 (d, J = 16 Hz, 1H), 7,87 (d, J = 2 Hz, 1H), 8,58 (d, J = 2 Hz, 1H). ESIMS (MH+): 279.

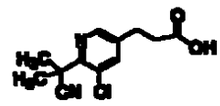
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Etapa 4:Éster etílico del ácido 3-[5-cloro-6-(ciano-dimetil-metil)-piridin-3-il]-propiónico



A una solución de éster etílico del ácido 3-[5-cloro-6-(ciano-dimetil-metil)-piridin-3-il]-acrílico (0,74 g, 2,65 mmol) de la etapa 3 anterior se le añadió etanol (10 ml) y $Pd(OH)_2/C$ (0,37 g). La reacción se puso en una atmósfera de hidrógeno usando un globo cargado con hidrógeno. La suspensión se agitó vigorosamente durante 1 hora. La reacción se filtró para retirar todos los sólidos y el líquido se concentró hasta dar un sólido que se usó en la siguiente reacción sin purificación adicional. ^1H RMN (400 MHz, $CDCl_3$): δ 1,25 (t, J = 7,7 Hz, 3 H), 1,85 (s, 6 H), 2,62-2,66 (m, 2 H), 2,92-2,98 (m, 2 H), 4,15 (q, J = 14, 7,7 Hz, 2 H), 7,61 (d, J = 2 Hz, 1H), 8,3 (d, J = 2 Hz, 1H). ESIMS (MH+): 289.

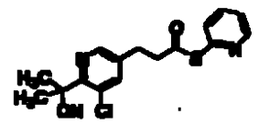
Etapa 5: Ácido 3-[5-cloro-6-(ciano-dimetil-metil)-piridin-3-il]-propiónico



A una solución agitada de éster etílico del ácido 3-[5-cloro-6-(ciano-dimetil-metil)-piridin-3-il]-propiónico (0,68g, 2,43 mmol) de la etapa 4 anterior en 1:1 de THF/H_20 (4 ml) se le añadió NaOH 2 N (2,43 ml). La solución resultante se agitó a 60°C durante 1 hora. Los disolventes se retiraron y el residuo se repartió entre acetato de etilo y ácido cítrico al 10% y se extrajo. La fase orgánica se lavó con salmuera (50 ml), se secó sobre Na_2SO_4 y se evaporó. El residuo se solidificó hasta dar un sólido blanco y se usó sin purificación adicional, (0,39 g, 64%) en forma de un sólido blanco. ESIMS (MH): 251.

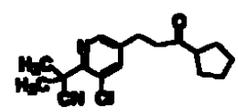
Etapa 6: S-Piridin-2-il éster del ácido 3-ciclohexil-tiopropiónico

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620



Se combinaron sucesivamente ácido 3-[5-cloro-6-(ciano-dimetil-metil)-piridin-3-il]-propiónico (0,39 g, 1,54 mmol) de la etapa 5 anterior, trifenilfosfina (0,53 g, 2,01 mmol) y disulfuro de 2,2'-dipirilo (0,44 g, 2,01 mmol) en CH_2Cl_2 (7 ml). La mezcla de reacción se agitó durante 4 horas. Los disolventes se retiraron y el residuo se purificó por cromatografía en columna ultrarrápida (EtOAc al 0-50% en hexanos) para dar el producto en forma de un sólido blanco. ESIMS (MH+): 346.

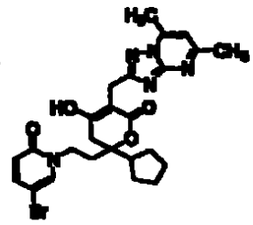
Etapa 7: 2-[3-cloro-5-(3-ciclopentil-3-oxo-propil)-piridin-2-il]-2-metil-propionitrilo



Se añadió bromuro una solución 2 M de ciclopentilmagnesio en éter (0,54 ml,1,10 mmol) a una solución enfriada a -78°C de S-piridin-2-il éster del ácido 3-ciclohexil-tiopropiónico (0,38 g, 1,10 mmol), de la etapa 6 anterior y se disolvió en THF (5 ml). La mezcla de reacción se agitó durante 2 min a -78°C y después se calentó a temperatura ambiente. La reacción se interrumpió con HCl 1 N y se extrajo con EtOAc. La capa orgánica se lavó con $NaHCO_3$ saturado y salmuera, se secó sobre Na_2SO_4 y se concentró. El residuo se purificó por cromatografía sobre gel de sílice (EtOAc al 0%-30% en hexanos) para dar el compuesto del título en forma de un aceite transparente (0,25 g, 76%). ^1H RMN (400 MHz, $CDCl_3$): δ 1,62-1,8 (m, 9H), 1,84 (s, 6 H), 2,78-2,92 (m, 4 H), 7,58 (s, 1H), 8,31 (s, 1H). ESIMS (MH+): 305.

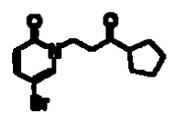
Ejemplo B(30): 5-Bromo-1-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)piridin-2(1H)-ona

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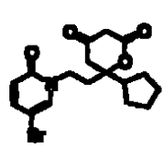
El compuesto del título se preparó de una forma análoga al ejemplo A(101), sustituyendo 5-bromo-1-[2-(2ciclopentil-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)-etil]-1H-piridin-2-ona en lugar de {4-[2-(2-ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]-2-etil-fenil)-acetonitrilo. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,33-1,70 (m, 9H), 2,07-2,25 (m, 2 H), 2,53 (s, 3 H), 2,56 (s, 3 H), 2,69 (s, 1H), 3,68-3,82 (m, 2 H), 3,82-4,00 (m, 2 H), 6,32-6,35 (m, 1H), 7,01 (s, 1H), 7,47-7,51 (m, 1H), 8,01-. 8,02 (m, 1H). Análisis calculado para $C_{28}H_{28}BrN_5O_4.1,2H_20$: C,53,23; H,5,43; N, 12,42, Encontrado: C,53,30; H,5,32; N, 12,03.

Etapa 1: 5-Bromo-1-(3-ciclopentil-3-oxo-propil)-1H-piridin-2-ona



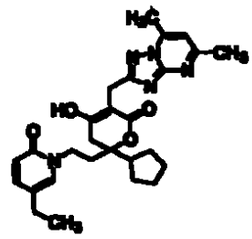
A una solución de 5-Bromo-1H-piridin-2-ona (0,53g, 3 mmol) y 1-ciclopentil-propenona (0,38 g, 3 mmol) en acetonitrilo anhidro/DMF (10 ml/5 ml) se le añadió CsF (46 mg, 0,3 mmol). La reacción se agitó a temperatura ambiente durante 4,5 horas. El disolvente se retiró al vacío y la mezcla se purificó por cromatografía en columna ultrarrápida (SiO_2, EtOAc en hexanos) para producir el producto deseado (400 mg, 45% de rendimiento). ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,56-1,80 (m, 9H), 2,98-3,02 (m, 2 H), 4,11-4,15 (m, 2 H), 6,44-6,47 (m, 1H), 7,32-7,36 (m, 1H), 7,61-7,62 (m, 1H).

Etapa 2: 5-Bromo-1-[2-(2-ciclopentil-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)-etil]-1H-piridin-2-ona



Se trató acetoacetato de metilo (0,44 ml, 4,04 mmol) disuelto en THF a 0°C con NaH (60%, 162 mg) y se agitó a esta temperatura durante 10 minutos antes de enfriarse adicionalmente a -40°C. Se añadió lentamente n-BuLi (2,5 M en hexanos, 1,6 ml) y se continuó agitando durante 10 minutos antes de que se añadiera 5-bromo-1-[2-(2-ciclopentil-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)-etil]-1H-piridin-2-ona (400 mg, 1,35 mmol) en forma de una solución en THF. La solución se calentó lentamente a temperatura ambiente y se agitó durante 2 horas más antes de inactivarse por la adición de H20. La mezcla se extrajo con EtOAc y la fase orgánica se lavó con salmuera y se secó sobre $MgSO_4$. El disolvente se retiró al vacío y el producto bruto se usó directamente en la siguiente etapa. El producto bruto de la etapa previa se disolvió en THF y se trató con NaOH 0,1 N (5 ml) durante 15 horas. La reacción se acidificó a pH 1 con HCl 1,0 N y se extrajo con EtOAc. La fase orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío para producir el producto deseado (220 mg, 43% en dos etapas). ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,39-1,82 (m, 9 H), 2,10-2,24 (m, 2 H), 2,77-2,89 (m, 2 H), 3,41-3,57 (m, 2 H), 3,92-4,15 (m, 2 H), 6,46-6,49 (m, 1H), 7,35-7,40 (m, 2H).

Ejemplo B(31): 1-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-5-etilpiridin-2(1H)-ona



El compuesto del título se preparó de una forma análoga al ejemplo B(30), sustituyendo 5-etil-1H-piridin-2ona en lugar de 5-bromo-1H-piridin-2-ona. ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,38 (t, J = 7,5 Hz, 3H), 1,61-1,97 (m, 9H), 2,31-2,42 (m, 2H), 2,53-2,63 (m, 2H), 2,77 (s, 3 H), 2,79 (s, 3 H), 2,88-3,01 (m, 2 H), 3,93-4,01 (m, 2H), 4,25 (s, 1H), 6,54-6,57 (m, 1H), 7,29 (s, 1H), 7,55-7,59 (m, 1H), 7,70-7,71 (m, 1H).

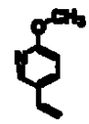
Etapa 1: 1-(6-Metoxi-piridin-3 il)-etanol

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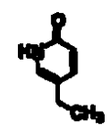
A una solución de 5-bromo-2metoxi-piridina (19,3 g, 193 mmol) en Et_2O anhidro (200 ml) a -78°C se le añadió n-BuLi (2,5 M en hexanos,50 ml) durante 30 min. La mezcla resultante se agitó a esta temperatura durante 30 minutos más antes de la adición de acetaldehído (5 ml). La reacción se calentó lentamente a la temperatura ambiente y el disolvente se retiró al vacío. El residuo se purificó por cromatografía en columna ultrarrápida para producir el producto deseado (14,3 g, 91% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,50 (d, J = 8,0 Hz, 3 H), 3,93 (s, 3 H), 4,87-4,92 (m, 1H), 6,75 (d, J = 8,0 Hz, 3 H), 7,63-7,66 (m, 1H), 8,12-8,14 (m, 1H).

Etapa 2: 2-Metoxi-5-vinil-piridina



A una solución de 1-(6-metoxi-piridin-3-il)-etanol (14,3 g, 93,5 mmol) en THF anhidro se le añadió trietilamina (32,3 ml), seguido de MsCl (8,6 ml, 112 mmol). La mezcla resultante se agitó a temperatura ambiente durante 15 horas antes del filtrado a través de una capa de celite. El filtrado se concentró al vacío y el residuo se purificó por cromatografía en columna ultrarrápida para producir el producto deseado (4,7 g, 37% de rendimiento). ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,94 (s, 3 H),5,20-5,23 (m, 1H),5,61-5,67 (m, 1H), 6,60-6,78 (m, 2 H), 7,67-7,72 (m, 1H), 8,12 (s, 1H).

Etapa 3: 5-etil-1H-piridin-2-ona

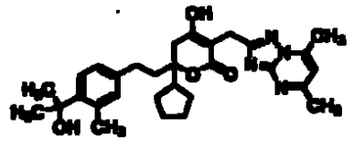


A una solución de 2-metoxi-5-vinil-piridina (2 g) en MeOH anhidro se le añadió Pd/C (10% en peso, 100 mg). La mezcla se agitó en una atmósfera de H2 durante 5

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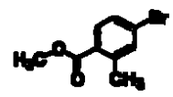
horas antes del filtrado a través de una capa de celite. El disolvente se retiró al vacío y el residuo se recogió directamente sin purificación adicional. El producto bruto de la etapa previa se disolvió en MeCN anhidro. A esta solución se le añadieron NaI (3,3 g, 21,9 mmol) y TMSCl (2,8 ml, 21,9 mmol). La mezcla resultante se calentó a 65°C durante 5 horas antes de filtrarse a través de una capa de celite. El filtrado se concentró al vacío y el residuo se purificó por cromatografía en columna ultrarrápida para producir el producto deseado (1,5 g, 83% de rendimiento). ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,17 (t, J = 7,5 Hz, 3 H), 2,39-2,49 (m, 2 H), 6,50-6,58 (m, 1H), 7,15 (s, 1H), 7,35-7,45 (m, 1H).

Ejemplo B(32): 6-ciclopentil-3-[(5,7,dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-[2-[4-(1-hidroxi-1-metiletil)-3-metilfenil]etil)-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo B(1) sustituyendo 2-(4-bromo-2-metilfenil)-propan-2-ol en lugar del bromuro en la etapa 2 del ejemplo B(2). ^{1}H RMN (400 MHz, $CDCl_3$): δ ppm 1,51 - 1,60 (m, J = 11,31,5,94,5,75 Hz, 6 H) 1,61 (s, 6 H) 1,63 - 1,65 (m, 2 H) 1,97 - 2,03 (m, J = 6,95,5,31,5,18 Hz, 2 H) 2,34 - 2,40 (m, 1H) 2,52 (s, 3 H) 2,55 (d, J = 7,83 Hz, 1H) 2,61 (dd, J = 11,62,5,81Hz, 3 H) 2,66 (s, 3 H) 2,78 (s, 3 H) 4,03 - 4,12 (m, 2 H) 6,83 (s, 1H) 6,90 - 6,94 (m, 2 H) 7,31 (d, J = 7,83 Hz, 1H). MS (ESI): 501 $(M+H-H_2O)^+$.

Etapa 1: Éster metílico del ácido 4-bromo-2-metil-benzoico

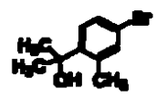


A una solución de ácido 4-bromo-2-metil-benzoico (10,0 g, 46,5 mmol) en metanol (100 ml) a temperatura ambiente se le añadió gota a gota ácido sulfúrico (conc., 1 ml). La solución se calentó a reflujo durante 16 h. La solución se retiró de la fuente de calor y se añadió ácido sulfúrico (conc., 0,5 ml). La solución se calentó a reflujo durante 2 h, después se enfrió a temperatura ambiente y se concentró *al vacío*. El residuo se disolvió en acetato de etilo y se lavó con bicarbonato sódico saturado y después con

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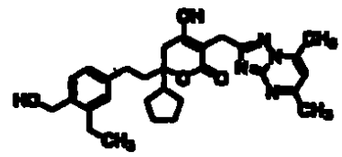
cloruro sódico saturado. La solución se secó ($MgSO_4$), se filtró y se concentró *al vacío* hasta dar un aceite incoloro bruto. La cromatografía ultrarrápida (SiO_2, acetato de etilo al 5%/hexano) dio el compuesto del título en forma de un aceite incoloro (9,2 g, 87%). ^1H RMN (400 MHz, $CDCl_3$): δ ppm 2,58 (s, 3 H) 3,88 (s, 3 H) 7,38 (dd, J = 8,46, 1,89 Hz, 1H) 7,42 (d, J = 1,52 Hz, 1H) 7,78 (d, J = 8,34 Hz, 1H).

Etapa 2: 2-(4-Bromo-2-metil-fenil)-propan-2-ol



A éster metílico del ácido 4-bromo-2-metil-benzoico (3,7 g, 15,9 mmol) en éter dietílico (10 ml) a 0°C en una atmósfera de N_2 se le añadió bromuro de etilmagnesio 3 N en éter dietílico (21 ml, 63 mmol). La mezcla se agitó durante 18 h a temperatura ambiente. La mezcla se vertió en ácido clorhídrico 1 N (ac., 10 ml) y se extrajo con acetato de etilo. La capa orgánica se lavó con cloruro sódico saturado, se secó ($MgSO_4$), se filtró y se concentró al vacío hasta dar un aceite incoloro bruto. La cromatografía ultrarrápida (SiO_2, acetato de etilo al 5%/hexano) dio el compuesto del título en forma de un aceite incoloro (2,6 g, 72%). ^1H RMN (300 MHz, $CDCl_3$): δ ppm 1,63 (s, 6 H) 2,56 (s, 3 H) 7,26 - 7,34 (*m*, 3 H).

Ejemplo B(33): 6-Ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-(2-[3-etil-4-(hidroximetil)fenil]etil)-4-hidroxi-5,6-dihidro-2H-piran-2-ona

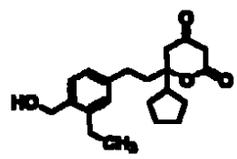


El compuesto del título se preparó de una forma análoga al ejemplo B(1) sustituyendo 6-ciclopentil-6-(2-[3etil-4-(hidroximetil)fenil]etil)dihidro-2H-piran-2,4(3H)-diona (Ejemplo B(34)) en lugar de 6-[2-(3-cloro-4-metanosulfonil-fenil)-etil]-6-ciclopentil-dihidro-piran-2,4-diona en ese ejemplo. Rendimiento (50 mg, 23%). ^1H RMN (300 MHz, $CDCl_3$): δ ppm 1,24 (t, J = 7,25 Hz, 3 H) 1,53 - 1,64 (m, 8 H) 1,96 - 2,02 (m, 2 H) 2,32 - 2,42 (m, 1H) 2,49 - 2,58 (m, 2 H) 2,65 (s, 3 H) 2,67 - 2,73 (m, 6 H) 2,78 (s, 3 H) 4,06 (s, 1H) 4,66 (s, 2 H) 6,83 (s, 1H) 6,94 - 7,01 (m, 2 H) 7,22 (d, J = 7,54 Hz, 1H). MS (ESI):

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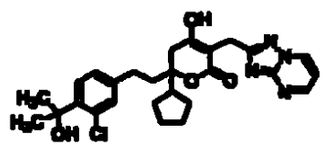
505 $(M+H)^+$.

Ejemplo B(34): 6-Ciclopentil-6-(2-[3-etil-4-(hidroximetil)fenil]etil)-dihidro-2H-piran-2,4(3H)-diona



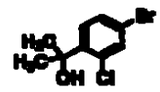
El compuesto del título se preparó de una forma análoga al ejemplo B(2) sustituyendo (4-bromo-2-etilfenil)-metanol en lugar del bromuro en ese ejemplo. ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,22 (t, J = 7,54 Hz, 3 H) 1,60 - 1,75 (m, 8 H) 1,91 - 2,04 (m, 3 H) 2,22 - 2,33 (m, 1H) 2,61 - 2,73 (m, 4 H) 2,76 (s, 2 H) 3,41 (s, 2 H) 4,68 (s, 2 H) 6,96 - 7,00 (m, 2 H) 7,28 (d, J = 8,29 Hz, 1H). MS (ESI): 367 $(M+Na)^+$.

Ejemplo B(35): 6-(2-[3-Cloro-4-(1-hidroxi-1-metiletil)fenil]etil)-6-ciclopentil-4-hidroxi-3-([1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil)-5,6-dihidro-2H-piran-2-ona



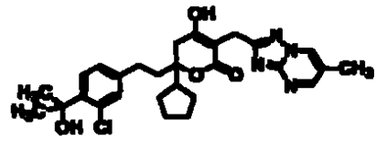
El compuesto del título se preparó de una forma análoga al ejemplo B(1) sustituyendo 2-(4-bromo-2-clorofenil)-propan-2-ol en lugar del bromuro en la etapa 2 del ejemplo B(2) de ese ejemplo y metoxi-[1,2,4]triazolo[1,5-a]pirimidin-2-il-metanol en lugar de 5,7-dimetil[1,2,4]triazolo[1,5-a)pirimidina-2-carbaldehído en el Ejemplo A(1). ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,58 (d, J-9,04 Hz, 8 H) 1,68 (s, 6 H) 1,94 - 2,05 (m, 2 H) 2,33 - 2,44 (m, 1H) 2,46 - 2,55 (m, 1H) 2,60 - 2,68 (m, 2 H) 2,70 - 2,80 (m, 1H) 4,11 (d, J = 2,45 Hz, 2 H) 7,01 (dd, J = 8,19, 1,79 Hz, 1H) 7,12 (d, J = 1,70 Hz, 1H) 7,14 - 7,21 (m. 1H) 7,51 (d, J = 8,10 Hz, 1H) 8,81 - 8,85 (m, 2 H). MS (ESI): 533 $(M+Na)^+$.

Etapa 1: 2-(4-Bromo-2-cloro-fenil)-propan-2-ol



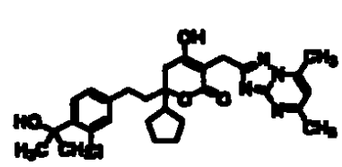
El compuesto del título se preparó de una forma análoga al ejemplo B(32) (Etapa 2) sustituyendo ácido 4-bromo-2-clorobenzoico en lugar de ácido 4-bromo-2-metilbenzoico. ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,71 (s, 6 H), 7,36-7,40 (m, 1H), 7,52 (m, 1H), 7,57-7,60 (m, 1H).

Ejemplo B(36): 6-{2-[3-Cloro-4-(1-hidroxi-1-metiletil)fenil]etil}-6-ciclopentil-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al B(35) sustituyendo 6-metil-[1,2,4]triazolo[1,5a]pirimidina-2-carbaldehído en lugar de metoxi-[1,2,4]triazolo[1,5-a]pirimidin-2-il-metanol en ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ ppm 1,57 (m, 6 H) 1,62 (s, 3 H) 1,68 (s, 6 H) 1,70 (d, J = 3,28 Hz, 3 H) 1,94 - 2,03 (m, 2 H) 2,34 - 2,43 (m, 1H) 2,47 (s, 3 H) 2,59 - 2,67 (m, 2 H) 2,74 (d, J = 17,94 Hz, 1H) 4,08 (d, J = 2,78 Hz, 1H) 7,01 (dd, P=7,96,1,64 Hz, 1H) 7,12 (d, J = 1,77 Hz, 1H) 7,50 (d, J = 8,08 Hz, 1H) 8,60 (d, J = 1,26 Hz, 1H) 8,68 (d, J = 2,27 Hz, 1H). MS (ESI): 547 $(M+Na)^+$.

Ejemplo B(37): 6-{2-[3-Cloro-4-(1-hidroxi-1-metiletil)fenil]etil}-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona

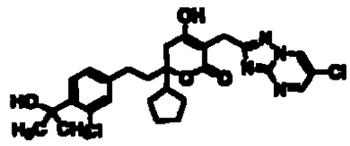


El compuesto del título se preparó de una forma análoga al ejemplo B(1) sustituyendo 2-(4-bromo-2-cloro-fenil)propan-2-ol en lugar del bromuro en la etapa 2 del

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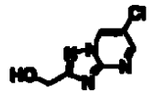
ejemplo B(2). ^{1}H RMN (300 MHz, $CDCl_3$): δ ppm 1,55 (s, 1H) 1,64 - 1,71 (m, 12 H) 1,94 - 2,03 (m, 2 H) 2,30 - 2,43 (m, 2 H) 2,50 (d, J = 17,90 Hz, 2 H) 2,58 - 2,64 (m, 2 H) 2,64 - 2,72 (m,5 H) 2,78 (s, 3 H) 4,07 (s, 2 H) 6,83 (s, 1H) 6,98 - 7,04 (m, 1H) 7,11 (d, J = 1,13 Hz, 1H) 7,50 (d, J = 8,10 Hz, 1H). MS (ESI): 561 $(M+Na)^+$. Análisis calculado para $C_{28}H_{35}ClN_4O_4$: 1,5 AcOH C, 61,09; H, 6,57; N, 8,91. Encontrado: C, 61,22; H, 6,50; N, 8,85.

Ejemplo B(38): 6-(2-[3-Cloro-4-(1-hidroxi-1-metiletil)fenil]etil)-4-[(6-cloro[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-ciclopentil-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo B(35) sustituyendo 6-cloro-[1,2,4]triazolo[1,5a]pirimidina-2-carbaldehído de la etapa 2 mostrada a continuación en lugar de metoxi[1,2,4]triazolo[1,5-a]pirimidin-2-il-metanol en ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6): δ ppm 1,34 (s, 1H) 1,48 - 1,59 (m, 10 H) 1,63 - 1,70 (m, 2 H) 2,03 (d, J = 19,96 Hz, 2 H) 2,34 - 2,44 (m, J = 8,84 Hz, 1H) 2,52 - 2,61 (m, J = 16,42 Hz, 3 H) 2,76 (d, J = 17,43 Hz, 1H) 3,29 - 3,41 (m, 3 H) 3,73 - 3,83 (m, 1H) 5,19 (s, 1H) 7,16 (dd, J = 3,92, 2,40 Hz, 2 H) 7,70 (d, J = 8,59 Hz, 1H) 8,85 (d, J = 2,53 Hz, 1H) 9,57 (d, J = 2,53 Hz, 1H). Análisis calculado para $C_{27}H_{30}Cl_2N_4O_4$: H_2O C,57,55; H,5,72; N, 9,94. Encontrado: C,57,57; H,5,81; N, 9,72.

Etapa 1: (6-Cloro[1,2,4]triazolo[1,5-a]pirimidin-2-il)metanol

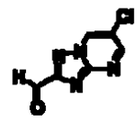


A una suspensión de (5-amino-1H-[1,2,4]triazol-3-il)-metanol (28,5 g, 150 mmol, de la etapa 6 del ejemplo A(1)) en ácido acético se le añadió cloromalonaldehído (16 g, 150 mmol). La mezcla se calentó a 80°C durante 4 horas. Después de la refrigeración de la solución, el producto cristalizó en forma de un sólido blanco (25,5 g, 92%). ^{1}H RMN (300 MHz, DMSO-d_6): δ 4,67 (s, 2 H),5,62 (s, 1H), 8,84 (d, J = 2,45 Hz, 1H), 9,81

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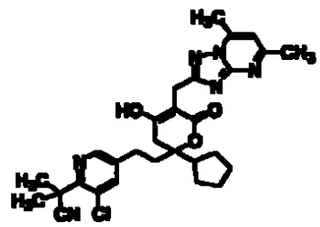
(d, J = 2,45 Hz, 1H).

Etapa 2: 6-Cloro[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído



Una mezcla de (6-cloro(1,2,4]triazolo[1,5-a]pirimidin-2-il)metanol (9,86 g,53,4 mmol), TEMPO (626 mg, 7,2 mmol) y diacetato de yodobenceno (18,9 g,59 mmol) en CH_2Cl_2 (75 ml) se agitó a temperatura ambiente durante 2 horas. Una vez que se consideró que la reacción se había completado, se añadió lentamente metil-terc-butil éter (50 ml) para precipitar el producto en forma de un sólido blanco (8,72 g, 90%). ^{1}H RMN (300 MHz, $CDCl_3$) δ: 8,93 (d, J = 2,45 Hz, 1H), 8,99 (d, J-2,64 Hz, 1H), 10,25 (s, 1H). MS (APCI): 183,0, 195,0 ($M+H^+$).

Ejemplo B(39): 2-[3-Cloro-5-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)piridin-2-il]-2-metilpropanonitrilo

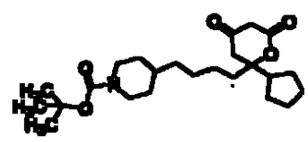


El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 2-(3-chloro-5-[2-(2ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)etil]piridin-2-il)-2-metilpropanonitrilo (Ejemplo B(29) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]dihidro-piran-2,4-diona de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6): δ 1,22-1,54 (m, 10 H), 1,59 (s, 6 H), 1,90-2,02 (m, 1H), 2,30-2,35 (m, 8 H), 2,37-2,59 (m, 2 H), 3,54 (d, J = 16 Hz, 1H), 3,64 (d, J = 16 Hz, 1H), 6,85 (s, 1H), 7,74 (s, 1H), 8,27 (s, 1H), 11 (s, 1H). . ESIMS (MH+): 549.

Ejemplo B(40): 4-[4-(2-Ciclopentil-4,6-dioxotetrahidro-2H-piran-2il)butil]piperidina-

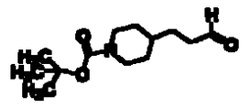
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1-carboxilato de terc-butilo



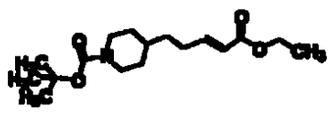
El compuesto del título se preparó de forma análoga al ejemplo B(2) sustituyendo éster terc-butílico del ácido 4-(5-ciclopentil-5-oxopentil)-piperidina-1-carboxílico de la etapa 6 mostrada a continuación en lugar de 3-(3cloro-4-metanosulfonil-fenil)-1-ciclopentil-propan-1-ona de ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,06-1,69 (m, 29H), 2,05-2,22 (m, 2H), 2,58-2,78 (m, 4H), 3,40 (s, 2H), 4,0-4,11 (m, 2H). ESIMS (MH+): 422.

Etapa 1: Éster terc-butílico del ácido 4-(3-oxo-propil)-piperidina-1-carboxílico



El compuesto del título se preparó de forma análoga a la etapa 2 del ejemplo B(29) sustituyendo éster terc-butílico del ácido 4-(3hidroxi-propil)-piperidina-1-carboxílico en lugar de 2-(3-cloro-5-hidroximetil-piridin-2-il)-2-metil-propionitrilo en ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,071,17 (m, 2H), 1,34-1,43 (m, 1H), 1,45 (s, 9H), 1,55-1,67 (m, 4H), 2,45-2,50 (m, 2H), 2,62-2,71 (m, 2H), 4,09-4,14 (m, 2H), 9,78 (s, 1H). ESIMS (MH+): 242.

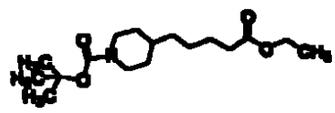
Etapa 2: Éster terc-butílico del ácido 4-(4-etoxicarbonil-but-3-enil)-piperidina-1-carboxílico



El compuesto del título se preparó de una forma análoga a la etapa 3 del ejemplo B(29) sustituyendo éster terc-butílico del ácido 4-(3-oxopropil)-piperidina-1-carboxílico de la etapa 1 anterior, en lugar de 2-(3-cloro-5-formil-piridin-2-il)-2-metil-

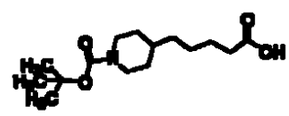
propionitrilo de ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 0,95-1 .08 (m, 2H), 1,21 (t, J = 7,2 Hz, 3 H), 1,32-1,35 (m, 3H), 1,38 (s, 9H), 1,56-1,60 (m, 2H), 2,092,19 (m, 2H), 2,5-2,83 (m, 2H), 3,97-3,99 (m, 2H), 4,11 (q, J = 7,2 Hz, 2 H),5,74 (dd, J = 15,6, 1,5 Hz, 1H), 6,82-6,93 (m, 1H). ESIMS (MH+): 312.

Etapa 3: Éster terc-butílico del ácido 4-(4-etoxicarbonil-butil)-piperidina-1-carboxílico



El compuesto del título se preparó de una forma análoga a la etapa 4 del ejemplo B(29) sustituyendo éster terc-butílico del ácido 4-(4etoxicarbonil-but-3-enil)-piperidina-1-carboxílico de la etapa 2 anterior, en lugar de éster etílico del ácido 3-[5-cloro-6-(ciano-dimetil-metil)-piridin-3-il]-acrílico. ^{1}H RMN (400 MHz, $CDCl_3$): δ 0,99-1,12 (m, 2H), 1,23-1,40 (m, 8H), 1,45 (s, 9H), 1,561,66 (m, 4H), 2,27-2,32 (m, 2H), 2,61-2,70 (m, 2H), 4,04-4,16 (m, 4H). ESIMS (MH+): 314.

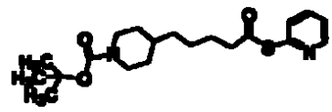
Etapa 4: Éster terc-butílico del ácido 4-(4-carboxi-butil)-piperidina-1-carboxílico



El compuesto del título se preparó de una forma análoga a la etapa 5 del ejemplo B(29) sustituyendo éster terc-butílico del ácido 4-(4etoxicarbonil-butil)-piperidina-1-carboxílico de la etapa 3 anterior, en lugar de éster etílico del ácido 3-[5-cloro-6-(ciano-dimetil-metil)-piridin-3-il]-propiónico en ese ejemplo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,07-1,39 (m. 7H), 1,45 (s, 9H), 1,59-1,70 (m, 4H), 2,33-2,38 (m, 2H), 2,64-2,68 (m, 2H), 4,09-4,12 (m, 2H). ESIMS (MH-): 284.

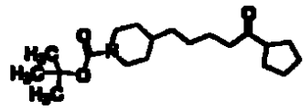
Etapa 5: Éster terc-butílico del ácido 4-[4-(piridin-2-ilsulfanilcarbonil)-butil]-piperidina-1-carboxílico

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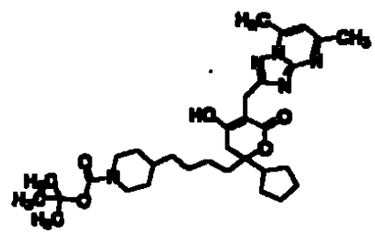
El compuesto del título se preparó de una forma análoga a la etapa 6 del ejemplo B(29) sustituyendo éster terc-butílico del ácido 4-(4-carboxibutil)-piperidina-1-carboxílico de la etapa 4 anterior, en lugar de ácido 3-[5cloro-6-(ciano-dimetil-metil)-piridin-3-il]-propiónico de ese ejemplo. ESIMS (MH+): 379.

Etapa 6: Éster terc-butílico del ácido 4-(5-ciclopentil-5-oxo-pentil)-piperidina-1-carboxílico



El compuesto del título se preparó de una forma análoga a la etapa 7 del ejemplo B(29) sustituyendo éster terc-butílico del ácido 4-[4-(piridin2-ilsulfanilcarbonil)-butil]-piperidina-1-carboxílico de la etapa 5 anterior, en lugar de S-piridin-2-il éster del ácido 3-ciclohexil-tiopropiónico. ^{1}H RMN (400 MHz, $CDCl_3$): δ 1-1,42 (m, 8H), 1,45 (s, 9H), 1,50-1,84 (m, 14H), 2,42-2,46 (m, 2H), 2,62-2,7 (m, 2H), 2,82-2,87 (m, 1H). ESIMS (MH+): 337.

Ejemplo B(41): 4-(4-(2-Ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}butil)piperidina-1-carboxilato de terc-butilo

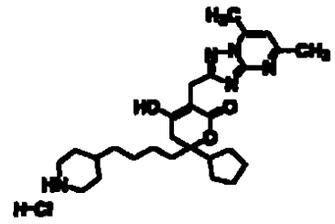


El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 4-[4-(2ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il)butil]piperidina-1-carboxilato de terc-butilo (ejemplo B(40)) en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-

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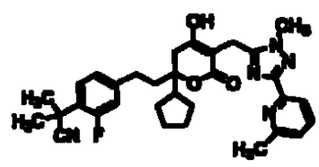
fenil)-etil]-dihidro-piran-2,4diona de ese ejemplo. ^{1}H RMN (400 MHz, DMSO-d_6): δ 0,76-1,50 (m, 29 H), 1,90-1,94 (m, 4 H), 2,27-2,6 (m, 8 H), 3,54-3,74 (m, 4H), 6,92 (s, 1H), 10,62 (s, 1H). ESIMS (MH+): 582.

Ejemplo B(42): 6-Ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-(4-piperidin-4-ilbutil)-5,6-dihidro-2H-piran-2-ona



Se disolvió 4-(4-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}butil)piperidina-1-carboxilato de terc-butilo (ejemplo B(41)) (0,47 g, 0,8 mmol) en dioxano (1 ml) y HCl 4 N en dioxano (1 ml). La reacción se agitó durante una noche a temperatura ambiente. Los disolventes se retiraron y el residuo se purificó usando un sistema Dionex (CH_3CN al 30-70%/H_2O (AcOH al 0,1%). H RMN (400 MHz, DMSO-d_6): δ 1,37-1,70 (m, 20 H), 2,63-2,85 (m, 12 H), 3,69-3,95 (m, 4H), 7,98 (s, 1H), 11,12 (s, 1H). Análisis calculado para $C_{27}H_{39}N_5O_3 \cdot 1,0$ HCl.1,5 H_2O: C,59,49; H, 7,95; N, 12,85, Encontrado: C,59,60; H, 8,04; N, 12,95. ESIMS (MH+): 482.

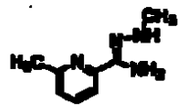
Ejemplo B(43): 2-{4-[2-(2-Ciclopentil-4-hidroxi-5{[1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-il]metil}-6-oxo-3,6-dihidro-2H-piran-2-il)etil]-2-fluorofenil}-2-metilpropanonitrilo



Una solución de 2-{4-[2-(2-ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]-2-fluoro-fenil)-2-metil-propionitrilo (1,0 g, 2,70 mmol, de la etapa 3 del ejemplo A(84) en isopropanol caliente (50°C) (7 ml) se trató con $(CH_3)_2NHBH_3$ (175 mg, 2,97 mmol, 1,1 equiv) y después con una solución de hidrocloruro de 1-metil-3-(6-metilpiridin-2-il)-1H-

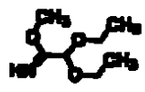
1,2,4-triazol-5-carbaldehído hidrato (762 mg, 2,97 mmol, 1,1 equiv, de la etapa 4 mostrada a continuación) en isopropanol (4 ml) que contenía trietilamina (301 mg, 2,97 mmol, 1,1 equiv). La mezcla de reacción se agitó calentando a 47-50°C durante 18 h. La mezcla de reacción se trató con 1,1 equiv de HCl acuoso 1 M y se concentró *al vacío* para producir una resina oleosa. Ésta se diluyó con agua y se extrajo con diclorometano que contenía metanol al 10% (3 x 30 ml). El extracto se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se trituró con acetato de etilo/cloruro de metileno caliente, se filtró, se lavó con éter frío y se secó, produciendo 584 mg (38%) del producto del título. ^{1}H RMN (400 MHz, DMSO-d_6): δ 1,36-1,71 (m, 14 H), 2,05 (m, 2 H), 2,48 (m, 1H), 2,46 (s, 3 H), 2,63 (m, 3 H), 2,78 (d, J = 17,9 Hz, 1H), 3,67(d, J = 15,7 Hz, 1H), 3,74(d, J = 15,7 Hz, 1H), 3,91 (s, 3 H), 6,99(d, J = 8,1Hz, 1H), 7,10-7,20 (m, 3 H), 7,57 (m, 2 H), 11,22 (s, 1H). LC-MS (APCI) *calculado para* $C_{32}H_{39}FN_8O_3$: 557,28, *encontrado* ($M+H^+$): 558,40 m/z.

Etapa 1: N',6-Dimetilpiridina-2-carbohidrazonamida



Se mezclaron 6-metilpiridina-2-carbonitrilo (45,3 g, 0,384 mol) y metilhidrazina (94 ml,5,30 mol) con etanol (200 ml). La mezcla se agitó a temperatura ambiente durante una noche y después se añadió una porción adicional (18 ml, 1,00 mol) de metilhidrazina y la mezcla se agitó durante 16 h más. La mezcla después se evaporó para dar 58,0 g de N',6-dimetilpiridina-2carbohidrazonamida en bruto (~92% de rendimiento), que se usó en la siguiente etapa de la síntesis sin purificación adicional.

Etapa 2: 2,2-Dietoxietanimidoato de metilo

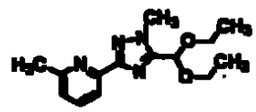


Una solución de dietoxiacetonitrilo (75 g, 0,579 mol) en metanol (210 ml) se añadió a temperatura ambiente a una solución de metóxido sódico (28,3 g, 0,522 mol) en metanol (450 ml). La mezcla se agitó durante una noche y después el metanol se evaporó cuidadosamente (producto volátil). El residuo se diluyó con diclorometano (200

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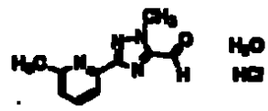
ml) y agua (300 ml). La capa orgánica se separó la capa acuosa se extrajo con diclorometano (2 x 150 ml). La capa orgánica combinada se secó sobre Na_2SO_4 y se evaporó para dar 83 g de 2,2dietoxietanimidoato de metilo en bruto (~90% de rendimiento).

Etapa 3: 2-[5-(Dietoximetil)-1-metil-1H-1,2,4-triazol-3-il]-6-metilpiridina



Se disolvió 2,2-dietoxietanimidoato o de metilo (42 g, 0,26 mol) en metanol (200 ml) y una solución del compuesto N,6-dimetilpiridina-2-carbohidrazonamida (43 g, 0,25 mol) en metanol (200 ml) mientras se enfriaba con un baño de agua, seguido de la adición de ácido acético (22 ml, 0,37 mol). La mezcla se agitó a temperatura ambiente durante 3 h y después se añadió K_2CO_3 (10 g, 0,071 mol). La mezcla se agitó durante 10 min y después se evaporó el metanol. El residuo se agitó con una solución de K_2CO_3 (20 g) en agua (200 ml) y se extrajo con éter (2 x 150 ml). La capa orgánica se lavó con agua y después con una solución saturada de NaCl, se secó sobre Na_2SO_4 y se evaporó. El residuo (62 g) se purificó por cromatografía sobre una columna de gel de sílice para producir 39,5 g (57%) del producto del título.

Etapa 4: Hidrocloruro de 1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-carbaldehído hidrato

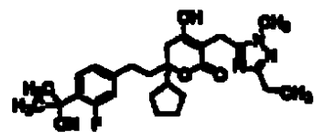


Una mezcla de 2-[5-(dietoximetil)-1-metil-1H-1,2,4-triazol-3-il]-6-metilpiridina (38 9, 0,1377 mol), agua (92 ml) y HCl concentrado (23 ml, 0,276 mol) se calentó a 70-80°C durante 2 h. La solución resultante se co-evaporó cuatro veces con agua usando un vacío creado con un aspirador de agua y después se secó *al vacío* a 60°C para dar 33,5 g (94,5%) del producto del título en forma de un hidrato unido covalentemente. Se obtuvo satisfactoriamente el análisis de C, H, N. ^{1}H RMN (400 MHz, D_2O+TFA): δ 2,90 (s, 3H), 4,13 (s, 3H), 6,38 (s, 1H), 7,94 (d, J = 8 Hz, 1H), 8,37 (d, J = 8 Hz, 1H), 8,58 (t, J = 8 Hz, 1H). LC-MS (APIES) calculado para $C_{10}H_{10}N_4O$: 202,09, encontrado ($M+H^+$):

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203,1; (M+18+H$^+$) 221,1 m/z.

Ejemplo B(44): 2-[4-(2-(2-ciclopentil-5-[(3-etil-1-metil-1H-1,2,4-triazol-5-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-fluorofenil]-2-metilpropanonitrilo



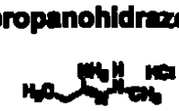
El compuesto del título se preparó de una forma análoga a la del ejemplo B(43) sustituyendo hidrocloruro de 3-etil-1-metil-1H-1,2,4-triazol-5-carbaldehído hidrato (etapa 4, mostrada a continuación) en lugar de 1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-carbaldehído. El producto se aisló por trituración con éter. Rendimiento: 552 mg 41%. ^{1}H RMN (400MHz, DMSO-d_6): δ 1,03 (d, J = 7,6 Hz, 3 H), 1,34-1,76 (m, 14 H), 2,06 (m, 2 H), 2,38 (m, 3 H), 2,60 (m, 3 H), 2,76 (d, J = 17,6 Hz, 1H), 3,53 (d, J = 15,9 Hz, 1H), 3,61 (d, J = 15,9 Hz, 1H), 3,73 (s, 3 H), 7,07 (d, J = 8,6 Hz, 1H), 7,13 (d, J13,1Hz, 1H), 7,35 (t, J = 8,6 Hz, 1H). LC-MS (APCI) calculado para $C_{28}H_{35}FN_4O_3$: 494,27, encontrado (M+H$^+$): 495,40 m/z.

Etapa 1: hidrocloruro de propanimidoato de metilo



Se añadió propiononitrilo (176 ml, 2,5 mol) a 0 °C a HCl 4 M en dioxano (690 ml). Se añadió gota a gota metanol absoluto (112 ml) a 0 °C y la mezcla se dejó en reposo a esta temperatura durante 1 hora y después en un frigorífico durante una noche. La suspensión cristalina resultante se trató con éter (700 ml). El precipitado cristalino se separó por filtración, se lavó con éter para retirar el HCl residual y se secó para dar el producto del título. Rendimiento: 226 g (73%).

Etapa 2: *Hidrocloruro de N*-metilpropanohidrazonamida



A una suspensión de hidrocloruro de propanimidoato de metilo (100 g, 0,803 mol) en metanol (400 ml) se le añadió gota a gota una solución de metilhidrazina (47 ml, 0,883 mol) a temperatura ambiente. La solución se dejó en reposo a temperatura ambiente durante 2 días y después se evaporó. El aceite resultante se lavó con THF (3

x 150 ml) y se secó para dar 84,1 g (61%) del producto del título bruto.

Etapa 3: 5-(Dietoximetil)-3-etil-1-metil-1H-1,2,4-triazol



Una solución de metóxido sódico (3,30 g, 0,0611 mol) en metanol (100 ml) se añadió a temperatura ambiente a una solución de dietoxiacetonitrilo (78,9 g, 0,611 mol) en metanol (600 ml). La mezcla resultante se agitó a temperatura ambiente durante una noche y se añadió hidrocloruro de N-metilpropanohidrazonamida bruto de la etapa 2 (84,1 g, ~0,60 mol) en metanol (200 ml). Se añadió acetato sódico anhidro (50,0 g, 0,61 mol) y la mezcla resultante se calentó a reflujo en una atmósfera de Ar durante 20 h. Después el metanol de evaporó y residuo oleoso negro se extrajo con éter (3 x 250 ml). La solución de éter se pasó a través de una capa de gel de sílice y el filtrado se evaporó. El residuo se destiló al vacío para dar 35,0 g (27%) del producto del título (p.e. 68 °C a 0,1 mm Hg). Nota: Hay una segunda fracción con un punto de ebullición más alto (15 g; p.e. 120 °C a 0,1 mm Hg) que es una impureza de triazol que contiene dos grupos acetal.

Etapa 4:Hidrocloruro de 3-etil-1-metil-1H-1,2,4-triazol-5-carbaldehído hidrato

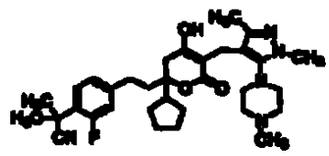


Una solución de 5-(dietoximetil)-3-etil-1-metil-1H-1,2,4-triazol de la etapa 3 (35,6 g, 0,187 mol) en HCl 3,6 M (150 ml) se calentó (60 °C) durante 10 h y después se evaporó a sequedad. El aceite residual se lavó con THF (3 x 100 ml) y después se trató con acetona seca (200 ml) provocando la cristalización. El producto se filtró y se secó, produciendo 18,8 g (59%) del producto del título. Se obtuvo satisfactoriamente el análisis de C, H, N. Según se observó por ^{1}H RMN el producto era una mezcla 60:40 de hidratos no covalentes (aldehído libre) y covalentes, respectivamente. ^{1}H RMN (400MHz, DMSO-d6): δ 1,22 (*m*, solapado, 3H), 2,67 (q, J = 7,8 Hz, 0,6 x 2H), 2,79 (q, J = 7,8 Hz, 0,4 x 2H), 3,96 (s, 0,4 x 3H), 4,04 (s, 0,6 x 3H), 6,21 (s, 0,4 x 1H), 8,35 (s a, 3H), 9,87 (s, 0,6 x 1H). LC-MS (APCI) calculado para $C_5H_9N_3O$: 139,07, encontrado ($M+H^+$): 140,1; ($M+18+H^+$) 158,1 m/z.

Ejemplo B(45): 2-(4-[2-(2-ciclopentil-5-([1,3-dimetil-5-(4-metilpiperazin-1-il)-1H-pirazol-4-il]metil}-4-hidroxi-oxo-3,6-dihidro-2H-piran-2 il)etil]-2-fluorofenil}-2-

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metilpropanonitrilo



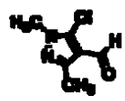
El compuesto del título se preparó de una forma análoga al ejemplo B(43) sustituyendo 1,3-dimetil-5-(4-metilpiperazin-1-il)-1H-pirazol-4-carbaldehído (etapa 3, mostrada a continuación) en lugar de 1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-carbaldehído y omitiendo la trietilamina. El producto se aisló por trituración con éter. Rendimiento: 1,0 g (64%). ^{1}H RMN (400MHz, DMSO-d6): δ 1,31-1,70 (m, 14 H), 1,90 (m, 2 H), 1,95 (s, 3 H), 2,25 (s, 3 H), 2,32 (m, 1H), 2,43 (m, 4 H), 2,57 (m, 3 H), 2,67 (d, J = 17,4 Hz, 1H), 3,06 (m, 4 H), 3,25 (d, J = 14,8 Hz, 1H), 3,32 (d, J = 14,8 Hz, 1H), 3,48 (s, 3 H), 6,99 (d, J = 8,1Hz, 1H), 7,08 (d, J = 13,1Hz, 1H), 7,35 (t, J = 8,3 Hz, 1H). LC-MS (APCI) calculado para $C_{33}H_{44}FN_5O_3$: 577,34, encontrado ($M+H^+$): 578,40 m/z.

Etapa 1: 1,3-dimetil-1H-pirazol-5-ol



A una solución de acetoacetato de etilo (50 g, 0,3846 mol) en metanol (280 ml) se le añadió gota a gota una solución de metilhidrazina (17,5 g, 0,38 mol) en metanol (20 ml) durante 20 min, produciendo un incremento en la temperatura hasta 45 °C. La mezcla de reacción se agitó durante una noche a temperatura ambiente. El metanol se retiró al vacío sobre un evaporador rotatorio para dar 50 g de la pirazolona del título en bruto que se usó en la siguiente etapa sin purificación.

Etapa 2: 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído

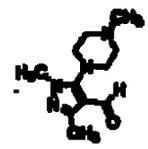


A DMF (33,29 ml, 0,456 mol) se le añadió cuidadosamente $POCl_3$ (134,16 g, 81,5 ml 0,874 mol) a 0 °C. La mezcla de reacción se diluyó con 1,2-dicloroetano (100 ml), después se trató con una solución de 1,3-dimetil-1H-pirazol-5-ol bruto (50 g, de la etapa 1) en dicloroetano (100 ml) con agitación continua a 0 °C. La mezcla se calentó a reflujo durante 3 h y después se dejó agitar durante una noche a temperatura ambiente. Con el fin de descomponer el reactivo de formilación, a la mezcla de reacción se le

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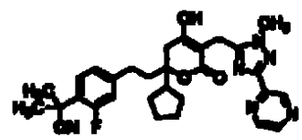
añadió gota a gota una solución de hidróxido sódico (91,2 g, 2,28 mol) en agua (200 ml) a 0 °C. La mezcla de reacción se diluyó con agua y se extrajo con diclorometano (3 x 250 ml). Los extractos orgánicos se lavaron con agua a pH neutro, se lavó con agua y después se secó con sulfato sódico. El disolvente se retiró al vacío para producir el producto del título (31,1 g,51% en total a partir de metilhidrazina) en forma de una sustancia cristalina amarilla.

Etapa 3: 1,3-Dimetil-5-(4-metilpiperazin-1-il)-1H-pirimazol-4-carbaldehído



A una solución de 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído (25,4 g, 0,16 mol) en HMPA (25 ml) y agua (25 ml) se le añadió 1-metilpiperazina (40 g, 0,4 mol, 2,5 equiv) y la mezcla se calentó a 120-125 °C durante 25 h. Una vez que se completó la adición, la mezcla de reacción se vertió en agua (500 ml) y se añadió carbonato potásico para hacer el medio fuertemente alcalino. La mezcla se extrajo con diclorometano (5 x 100 ml). Los extractos orgánicos combinados se lavaron dos veces con agua y se secaron con sulfato sódico y el disolvente se evaporó. El residuo se purificó cromatográficamente sobre gel de sílice con una elución en gradiente de diclorometano a metanol, produciendo 10,2 g (29%) del producto del título. Se obtuvo satisfactoriamente el análisis de C, H, N. ^{1}H RMN (400MHz, DMSO-d_6): δ 2,23 (s, 3H), 2,26 (s, 3H), 2,44 (m, 4H), 3,16 (m, 4H), 3,59 (s, 3H), 9,88 (s, 1H). LC-MS (API-ES) calculado para $C_{11}H_{16}N_4O$: 222,15, encontrado ($M+H^+$): 223,1 m/z.

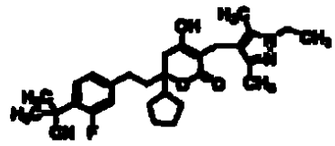
Ejemplo B(46): 2-[4-(2-(2-ciclopentil-4-hidroxi-6-[(1-metil-3-pirazin-2-il-1H-1,2,4-triazol-5-il)metil)-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2fluorofenil]-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo B(15) sustituyendo 2-(4-[2-(2- ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]-2-fluoro-fenil)-2-metil-propionitrilo (de la etapa del ejemplo A(84)) en lugar de 6-[2-(5-cloro-2,4-dimetoxi-fenil)-etil]-6-ciclopentil-dihidro-piran-2,4-diona. El producto se cromatografió sobre gel de sili-

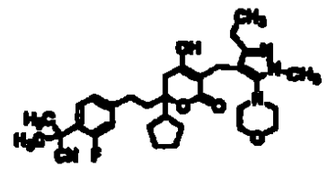
ce y se trituró con éter. Rendimiento = 201 mg (13%). ^{1}H RMN (400MHz, DMSO-de): δ 1,35-1,71 (m, 14 H), 2,02 (m, 2 H), 2,39 (s, 1H), 2,59 (m, 3 H), 2,75 (d, J = 17,4 Hz, 1H), 3,69 (d, J = 17,1Hz, 1H), 3,76 (d, J-17,1Hz, 1H), 3,94 (s, 3 H), 6,99 (d, J = 8,1Hz, 1H), 7,08 (d, J = 13,1Hz, 1H), 7,20 (t, J = 8,3 Hz, 1H), 8,6C (s, 1H), 8,64 (s, 1H), 8,97 (s, 1H). LC-MS (APCI) calculado para $C_{30}H_{33}FN_6O_3$: 544,63, encontrado ($M+H^+$) 545,30 m/z.

Ejemplo B(47): 2-[4{2-(2-ciclopentil-5-[(1-etil-3,5-dimetil-1H-pirazol-4-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2 il}etil)-2 fluorofenil]-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo B(43) sustituyendo 1-etil-3,5-dimetil-1H-pirazol-4-carbaldehído en lugar de 1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-carbaldehído y omitiendo la trietilamina. El producto se purificó por cromatografía sobre gel de sílice y trituración con éter. Rendimiento: 795 mg,58%. ^{1}H RMN (400MHz, DMSO-d6): δ 1,14 (t, J = 7,1Hz, 3 H), 1,28-1,62 (m, 8 H), 1,70 (s, 6 H), 1,82 (m, 2 H), 2,04 (s, 3 H), 2,11 (s, 3 H), 2,26 (m, 1H), 2,48-2,55 (m, 3 H), 2,69 (d, J = 17,6 Hz, 1H), 3,11 (d, J-14,6 Hz, 1H), 3,22 (d, J = 14,6 Hz, 1H), 3,84 (q, J = 7,3 Hz, 2 H), 6,93 (d, J = 9,6 Hz, 1H), 7,04 (d, J = 11,6 Hz, 1H), 7,34 (t, J = 8,6 Hz, 1H), 10,65 (s, 1H). LC-MS (APCI) calculado para $C_{30}H_{39}FN_3O_3$: 507,29, encontrado ($M+H^+$): 508,40 m/z.

Ejemplo B(48): 2-(4-(2-(2-ciclopentil-5-[(3-etil-1-metil-5-morfolin-4-il-1H-pirazol-4-il)metil]-4-hidroxi-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo B(43) sustituyendo 3-etil-1-metil-5-morfolin-4-il-1H-pirazol-4-carbaldehído (Etapa 3, mostrada a continuación) en lugar de 1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-carbaldehído y omitiendo la trietilamina. El producto se purificó por cromatografía sobre gel de sílice y se recristalizó en acetato de etilo/éter. Rendimiento: 486 mg (31%). ^{1}H RMN (400MHz,

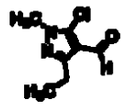
DMSO-d_6): δ 1,01 (t, J = 7,6 Hz, 3 H), 1,32-1,64 (m, 8 H), 1,70 (s, 6 H), 1,89 (m, 2 H), 2,36 (m, 2 H), 2,58 (m, 2 H), 2,67 (d, J = 17,6 Hz, 1H), 3,05 (s, 4 H), 3,26-3,41 (m, 4 H), 3,54 (s, 3 H), 3,63 (m, 4 H), 6,99 (d, J=9,3 Hz, 1H), 7,09 (d, J = 14,3 Hz, 1H), 7,35 (t, J = 8,3 Hz, 1H), 10,70 (s, 1H). LC-MS (APCI) calculado para C33H43FN4O4: 578,33, encontrado ($M+H^+$): 579,40 m/z.

Etapa 1: 3-etil-1-metil-1H-pirazol-5-ol



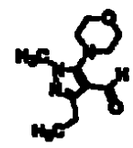
Se añadió gota a gota metilhidrazina (31,6 g, 0,687 mol) en metanol (100 ml) a una solución de 3-oxopentanoato de etilo (100 g, 0,694 mol) en metanol (280 ml) durante un periodo de 45 min, tiempo durante el cual la temperatura se incrementó a 45 °C. La mezcla de reacción después se dejó en agitación a temperatura ambiente durante una noche y después se evaporó, produciendo 84,5 g (97%) del producto del título.

Etapa 2: 5-Cloro-3-etil-1-metil-1H-pirazol-4-carbaldehído



Se añadió gota a gota $POCl_3$ (236,88 g, 1,543 mol, 144 ml) a 0 °C a DMF (59 g, 0,808 mol). La mezcla de reacción después se diluyó con diclorometano (200 ml) y se añadió 3-etil-1-metil-1H-pirazol-5-ol (84,5 g, de la etapa 1) mientras se agitaba a 0 °C. La mezcla se calentó a reflujo durante 3 h y después se agitó durante una noche a temperatura ambiente. Después de esto, se añadió rápidamente agua enfriada con hielo a 0°C (500 ml) a la mezcla de reacción con el fin de descomponer el agente de formilación. La capa orgánica se separó y la fase acuosa se extrajo varias veces con cloroformo. Después, las capas orgánicas se lavaron con una solución de K_2CO_3 para obtener un medio débilmente alcalino, se secaron sobre Na_2SO_4 y se evaporaron para dar 51,2 g de una sustancia oleosa. La masa de reacción residual se neutralizó con K_2CO_3 para obtener un medio débilmente ácido y se extrajo con cloroformo. Los extractos orgánicos se concentraron y el residuo se purificó por cromatografía (diclorometano) sobre gel de sílice para dar 71,3 g (62%) del producto del título.

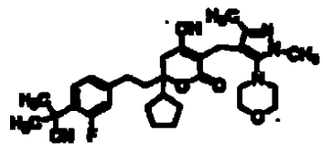
Etapa 3: 3-Etil-1-metil-5-morfolin-4-il-1H-pirazol-4-carbaldehído



Se añadieron morfolina (35,15 g, 0,4 mol) y agua (30 ml) con agitación a temperatura ambiente a una mezcla de 5-cloro-3-etil-1-metil-1H-pirazol-4-carbaldehído de la etapa 2 (35 g, 0,202 mol) en HMPA (30 ml). La mezcla de reacción se calentó a 90 °C durante 8 h, después se diluyó con agua y se extrajo con acetato de etilo (3 x 100 ml). Los extractos orgánicos se lavaron con agua para obtener un medio débilmente alcalino, se secaron sobre Na_2SO_4 y se evaporaron. El residuo se purificó por cromatografía (hexano/acetato de etilo) sobre gel de sílice para producir 37,2 g (82,6%) del producto del título. Se obtuvo satisfactoriamente el análisis de C, H, N.

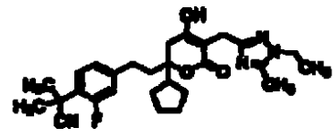
^{1}H RMN (400MHz, DMSO-d_6): δ 1,14 (t, J = 7,6 Hz, 3H), 2,71 (q, J = 7,6 Hz, 2H), 3,16 (m, 4H), 3,65 (s, 3H), 3,72 (m, 4H), 9,91 (s, 1H). LC-MS (API-ES) calculado para $C_{11}H_{17}N_3O_2$: 223,13, encontrado ($M+H^+$): 224,1 m/z

Ejemplo B(49): 2-[4-(2-{2-Ciclopentil-5-[(1,3-dimetil-5-morfolin-4il-1H-pirazol-4-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo



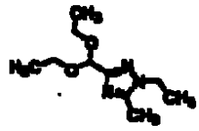
El compuesto del título se preparó de una forma análoga al ejemplo B(43) sustituyendo 1,3-dimetil-5-morfolin-4-il-1H-pirazol-4-carbaldehído en lugar de 1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-carbaldehído. Rendimiento: 448, 29%. ^{1}H RMN (400MHz, DMSO-d6): δ 1,32-1,64 (m, 8 H), 1,70 (s, 6 H), 1,90 (m, 2 H), 1,95 (s, 3 H), 2,32 (m, 1H), 2,58 (m, 3 H), 2,68 (d, J = 17,6 Hz, 1H), 3,04 (m, 4 H), 3,27 (d, J = 14,9 Hz, 1H), 3,30 (d, J = 14,9 Hz, 1H), 3,52 (s, 3 H), 3,62 (m, 4 H), 6,99 (d, J = 9,3 Hz, 1H), 7,09 (d, J = 14,3 Hz, 1H), 7,35 (t, J = 8,3 Hz, 1H), 10,73 (s, 1H). LC-MS (APCI) calculado para $C_{32}H_{41}FN_4O_4$: 564,31, encontrado ($M+H^+$): 565,40 m/z.

Ejemplo B(50): 2-[4-(2-{2-Ciclopentil-5-[(1-etil-5-metil-1H-1,2,4-triazol-3 il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2fluorofenil]-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo B(43) sustituyendo 1-etil-5-metil-1H-1,2,4-triazol-3-carbaldehído (etapa 2, mostrada a continuación) en lugar de 1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-carbaldehído y omitiendo la trietilamina. Rendimiento = 195 mg (14%). ^{1}H RMN (400MHz, DMSO-d_6): δ 1,15 (t, J = 7,3 Hz, 3 H), 1,37-1,71 (m, 14 H), 2,11 (m, 2 H), 2,24 (s, 3 H), 2,40 (m, 1H), 2,64 (m, 3 H), 2,74 (d, J = 17,4 Hz, 1H), 3,42 (d, J = 15,8 Hz, 1H), 3,52 (d, J = 15,6 Hz, 1H), 3,99 (q, J = 7,3 Hz, 2 H), 7,11 (m, 2 H), 7,35 (t, J = 8,3 Hz, 1H), 10,81 (s, 1H). LC-MS (APCI) calculado para $C_{28}H_{35}FN_4O_3$: 494,27, encontrado ($M+H^+$): 495,30 m/z.

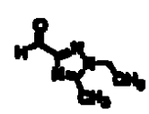
Etapa 1: 3-Dietoximetil-1-etil-5-metil-1H-[1,2,4]triazol



A una solución de NaOMe (24 ml, 25% en peso en MeOH, 0,105 mol, 4,3% en moles) en MeOH (2,4 l) se le añadió dietoxiacetonitrilo (310 g, 2,40 mol) y la mezcla de reacción se agitó a temperatura ambiente durante 24 h. El disolvente se retiró al vacío (300 mbar, 44 °C) y el residuo aceitoso pardo se disolvió en Et_2O (2,4 l). La solución orgánica se lavó con agua (3 x 500 ml) y salmuera (1 x 400 ml) y se secó sobre Na_2SO_4. El disolvente se retiró al vacío a 0 °C para producir 2,2-dietoxiethanimidoato de metilo (333,32 g, 86%) en forma de un líquido transparente. A una solución de NaOMe (25% en peso en MeOH, 424 g, 2 mol) y MeOH (2 L), se le añadió oxalato de etilhidrazina (150,14 g, 1 mol) y la mezcla se agitó durante 10 min. Se añadió 2,2-dietoxiethanimidoato de metilo (161,2 g, 1 mol) y la mezcla se agitó a temperatura ambiente durante 3 h en una atmósfera de nitrógeno. El producto, (1Z)-2,2-dietoxi-N-etiletanohidrazonamida se usó in situ. La (1Z)-2,2-dietoxi-N-etiletanohidrazonamida bruta se trató con hidrocloruro de acetimidato (109,6 g, 1 mol) y ácido acético glacial (90 g, 1,5 mol) y la mezcla se agitó a temperatura ambiente durante 24 h en una atmósfera de nitrógeno. La LCMS indicó que la reacción no se había producido después de 24 h. El disolvente se retiró al vacío de la mezcla de reacción y el residuo se mantuvo en el congelador. Después de 8 días el residuo se retiró del congelador, se calentó a temperatura ambiente y se trató con MeOH (1,5 L), ácido acético (85,7 ml) y HCl de acetimidato (98 g, 0,89 mol) en un nuevo recipiente y esta mezcla se agitó a temperatu-

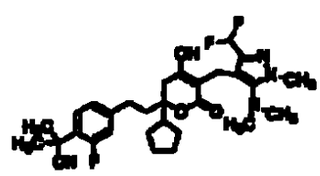
ra ambiente durante 24 h. La LCMS indicó que los materiales de partida se habían consumido y que estaba presente algo del producto deseado. El disolvente se retiró al vacío y al residuo se le añadió H_2O (1,5 l). La mezcla se extrajo con DCM (5 x 1 L) y las capas orgánicas combinadas se secaron sobre Na_2SO_4. El disolvente se retiró al vacío para producir 163 g de un aceite rojo bruto. El producto se purificó por cromatografía ultrarrápida usando MeOH al 2%/DMC como eluyente (RF=0,3) produciendo 56,86 g (23%) de 3-(dietoximetil)-1-etil-5-metil-1H-1,2,4-triazol en forma de un aceite rojo que tenía una pureza de 96% según mostró el análisis por ^{1}H RMN.

Etapa 2: 1-Etil-5-metil-1H-[1,2,4]triazol-3-carbaldehído



Una mezcla de 3-(dietoximetil)-1-etil-5-metil-1H-[1,2,4]triazol de la etapa 1 (56,86 g, 0,267 mol) y H_2O (300 ml) se trató lentamente con HCl acuoso al 35% (55,61 g, 0,534 mol) y la reacción se agitó a temperatura ambiente durante 24 h. La mezcla se lavó con DCM (2 x 200 ml). La fase acuosa se basificó a pH 13 con NaOH y se lavó con DCM (3 x 200 ml). Los extractos de DCM combinados se desecharon. La fase acuosa se neutralizó a pH 7 con HCl y se extrajo con DCM (3 x 200 ml). La fase orgánica de esta última extracción, que contenía el producto, se secó sobre Na_2SO_4 y el disolvente se retiró al vacío, produciendo 9,8 g (26%) de 1-etil-5-metil-1H-[1,2,4]triazol-3-carbaldehído que tenía una pureza de 96% según determinó el análisis por RMN. ^{1}H RMN (500 MHz, $CDCl_3$): δ 1,49 (t, .1=7,5 Hz, 3H), 2,51 (s, 3H), 4,20 (q, J = 7,5 Hz, 2H), 9,91 (s, 1H). ^{13}C RMN (125 MHz, $CDCl_3$): δ 12,1, 14,9, 44,4, 154,0, 159,2, 184,0. LC-MS (APCI) calculado para $C_5H_9N_3O$: 139,07, encontrado ($M+H^+$): 140,1 m/z. Anal calculado para $C_5H_9N_3O$: C,51,79; H, 6,52; N, 30,20; Encontrado: C,51,5; H, 6,38; N, 29,98.

Ejemplo B(51): 2-(4-[2-(2-Ciclopentil-5-[[3-(difluorometil)-5-(dimetilamino)-1-metil-1H-pirazol-4-il]metil]-4-hidroxi-oxo-3,6-dihidro-2H-piran-2 il)etil]-2 fluorofenil)-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo B(43) sustituyendo 3-(difluorometil)-5-(dimetilamino)-1-metil-1H-pirazol-4-carbaldehído (etapa 3,

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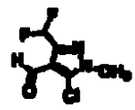
mostrada a continuación) en lugar de 1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-carbaldehído y omitiendo la trietilamina. Rendimiento: 142 mg (9%). ^{1}H RMN (400MHz, DMSO-d_6): δ 1,31-1,63 (m, 8 H), 1,70 (s, 6 H), 1,89 (m, 2 H), 2,32 (m, 1H), 2,57 (m, 3 H), 2,67 (m, 2 H), 2,74 (s, 6 H), 3,40 (d, J = 15,1Hz, 1H), 3,44 (d, J = 15,1Hz, 1H), 3,61 (s, 3 H), 6,98 (d, J = 9,3 Hz, 1H), 7,06 (d, J-13,1Hz, 1H), 7,34 (t, J = 8,3 Hz, 1H), 10,92 (s, 1H). LC-MS (APCI) calculado para $C_{30}H_{37}F_3N_4O_3$: 558,28, encontrado ($M+H^+$): 559,30 m/z.

Etapa 1: 3-(Difluorometil)-1-metil-1H-pirazol-5-ol



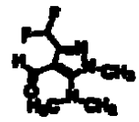
A una solución de 4,4-difluoro-3-oxobutanoato de metilo (64 g, 0,38 mol) en metanol (500 ml) se le añadió metilhidrazina (20,5 ml, 0,38 mol). La mezcla de reacción se dejó en agitación durante una noche a temperatura ambiente. Los volátiles se retiraron al vacío, se añadió tolueno (400 ml), la mezcla se evaporó de nuevo y se repitió este procedimiento. El residuo sólido resultante se purificó cromatográficamente sobre gel de sílice usando una mezcla de acetato de etilo/diclorometano (1:2, R_f = 0,35). El aceite resultante se cristalizó en éter (200 ml) y se secó al vacío de una bomba de membrana (10 mm Hg) durante 3 h para dar 28 g (49,8%) del producto del título.

Etapa 2: 5-Cloro-3-(difluorometil)-1-metil-1H-pirazol-4-carbaldehído



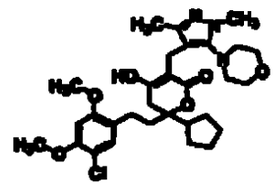
A DMF (40,84 g, 0,56 mol) se le añadió $POCl_3$ (104,4 ml, 1,12 mol) a 0 °C. Después de 30 min, al reactivo de Vilsmier resultante se le añadió 3-(difluorometil)-1-metil-1H-pirazol-5-ol de la etapa 1 anterior (69,1 g, 0,46 mol) y la mezcla se calentó a 80 °C durante 16 h. Después, la reacción se diluyó con diclorometano (400 ml) y se trató con una solución de carbonato potásico (780 g) en agua (2 l) a 0 °C. La capa orgánica se separó y la capa acuosa se extrajo con diclorometano (3 x 100 ml). Los extractos orgánicos combinados se lavaron con agua (500 ml), se pasaron a través de una capa de gel de sílice (10 x 10 cm) y se evaporaron. El residuo se cristalizó en éter (100 ml) y hexano (100 ml) para dar 69 g (77%) del producto del título.

Etapa 3: 3-(Difluorometil)-5-(dimetilamino)-1-metil-1H-pirazol-4-carbaldehído



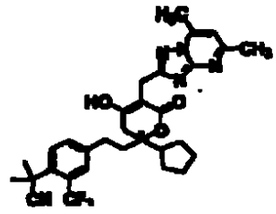
A una mezcla de 5-cloro-3-(difluorometil)-1-metil-1H-pirazol-4-carbaldehído (34 g, 0,17 mol) y HMPA (50 ml) se le añadió una solución acuosa al 40% de dimetilamina (66,3 ml). La mezcla de reacción se agitó durante 12 h a 50°C, se diluyó con agua (1 l) y el producto se extrajo con diclorometano (2 x 100 ml). Las capas orgánicas combinadas se secaron con sulfato sódico y se evaporaron. El residuo líquido se purificó cromatográficamente sobre gel de sílice usando diclorometano/acetato de etilo como eluyente (1:3, R_f = 0,25) para dar 17,81 g (51,6%) del producto del título. Se obtuvo satisfactoriamente el análisis de C, H, N. ^{1}H RMN (400 MHz, DMSO-d_6): δ 2,93 (s, 6H), 3,72 (s, 6H), 7,07 (t, J = 56 Hz, 1H), 9,94 (s, 1H). GC-MS calculado para $C_8H_{11}F2N3O$: 203,09, encontrado (M^+): 203 m/z.

Ejemplo B(52): 6-[2-(5-Cloro-2,4-dimetoxifenil)etil]-6-ciclopentil-3-[(1,3-dimetil-5-morfolin-4-il-1H-pirazol-4-il)methyq-4-hidroxi-5,6-dihidro-2H-piran-2-ona



El compuesto del título se preparó de una forma análoga al ejemplo B(15) usando 1,3-dimetil-5-morfolin-4-il-1H-pirazol-4-carbaldehído en lugar de dihidrocloruro de 2-metil-5-pirazin-2-il-2H-[1,2,4]triazol-3-carbaldehído monohidrato y omitiendo la trietilamina. El rendimiento obtenido en una escala de 0,78 mmol fue de 34 mg (7%). ^{1}H RMN (400MHz, $CDCl_3$): δ 1,18-1,83 (m, 8 H), 2,19 (s, 3 H), 2,28 (m, 1H), 2,47 (m, 3 H), 2,68 (m, 1H), 3,07 (m, 2 H), 3,21 (s, 3 H), 3,36 (s, 2 H), 3,69-3,81 (m, 14 H), 6,38 (s, 1H), 6,94 (s, 1H). LC-MS (APCI) calculado para $C_{30}H_{40}ClN_3O_8$: 573,26, encontrado ($M+H^+$): 574,20,576,20 m/z.

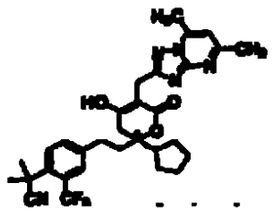
Ejemplo B(53): Enantiómero 1 de 2-[4-(2{2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-(trifluorometil)fenil]-2-metilpropanonitrilo



Enantiómero 1

El compuesto del título se separó del 2-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil)-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-(trifluorometil)fenil]-2-metilpropanonitrilo racémico (338 mg, Ejemplo B(28)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 50%). (151.32 mg, tiempo de retención 1,84 min, 100% ee)

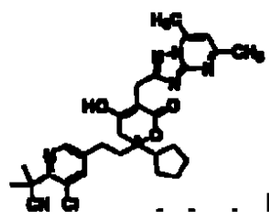
Ejemplo B(54): Enantiómero 2 de 2-[4-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il]etil)-2-(trifluorometil)fenil-2-metilpropanonitrilo



Enantiómero 2

El compuesto del título se separó del 2-[4(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)-2-(trifluorometil)fenil]-2-metilpropanonitrilo racémico (338 mg, Ejemplo B(28)) usando HPLC quiral (Chiralpak AS-H, 140 bar, MeOH al 50%). (239.86 mg, tiempo de retención 4,94 min, 100% ee)

Ejemplo B(55): Enantiómero 1 de 2-[3-cloro-5-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil)piridin-2 il-2-metilpropanonitrilo



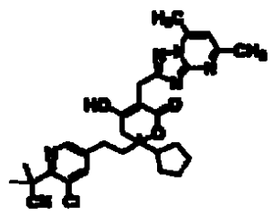
Enantiómero 1

El compuesto del título se separó del 2-[3-cloro-5-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-oxo-3,6-dihidro-2 H-piran-2-il)etil)piridin-2-il]-2-metilpropanonitrilo (75 mg, Ejemplo B(39)) usando HPLC quiral (Chi-

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raipak AS-H, 140 bar,55% MeOH). (11.37 mg, tiempo de retención 1,93 min, 91% ee)

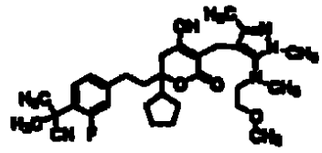
Ejemplo B(56): Enantiómero 2 de 2-[3-cloro-5(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2 il)metil-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2 il)etil)piridin-2-il]-2-metilpropanonitrilo



Enantiómero 2

El compuesto del título se separó del 2-[3-cloro-5-(2{2-ciclopentil-5-((5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-oxo-3,6-dihidro-2H-piran-2-il)etil)piridin-2-il]-2-metilpropanonitrilo racémico (75 mg, Ejemplo B(39)) usando HPLC quiral (Chiralpak AS-H, 140 bar,55% MeOH). (9.59 mg, tiempo de retención 4,32 min, 96% ee)

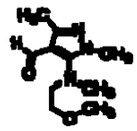
Ejemplo B(57): 2-(4-{2-[2-ciclopentil-4-hidroxi-5{{5-[(2-metoxietil)(metil)amino]-1,3-dimetil-1H-pirazolil}metil)-6-oxo-3,6-dihidro-2H-piran-2-il]etil}2-fluorofenil)-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo B(43) sustituyendo 5-[(2-metoxietil)(metil)amino]-1,3-dimetil-1H-pirazol-4-carbaldehído (etapa 1, mostrada a continuación) en lugar de 1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-carbaldehído y omitiendo la trietilamina. Rendimiento: 132 mg (8%). ^{1}H RMN (400MHz, DMSO-d_6): δ 1,31-1,70 (m, 14 H), 1,90 (m, 2 H), 1,95 (s, 3 H), 2,32 (m, 1H), 2,57 (m, 3 H), 2,67 (d, J = 17,6 Hz, 1H), 2,72 (s, 3 H), 3,14 (m, 2 H), 3,21 (s, 3 H), 3,25 (d, J = 5,5 Hz, 1H), 3,31 (m, 3 H), 3,49 (s, 3 H), 6,99 (dd, J = 8,2, 1,5 Hz, 1H), 7,09 (dd, J = 13,1, 1,5 Hz, 1H), 7,35 (t, J = 8,4 Hz, 1H), 10,67 (s, 1H). LC-MS (APCI) calculado para $C_{33}H_{43}FN_4O_4$: 566,71, encontrado ($M+H^+$): 567,40 m/z.

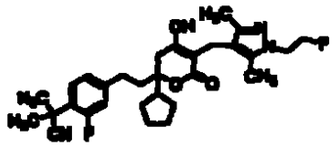
Etapa 1: 5-[(2-Metoxietil)(metil)amino]-1,3-dimetil-1H-pirazol-4-carbaldehído

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Una mezcla de 2-(metoxietil)metilamina (32,93 g, 40 ml, 0,37 mol),5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído (etapa 2 del ejemplo B(45)) (29,28 g, 0,185 mol), HMPA (25 ml) y agua (25 ml) se calentó a 120-125 °C durante 17 h. La mezcla de reacción se vertió en agua (500 ml) y la mezcla resultante se basificó con carbonato potásico. La mezcla se extrajo con acetato de etilo (5 x 100 ml). Los extractos orgánicos combinados se lavaron dos veces con agua, se secaron con sulfato sódico, se filtraron y el disolvente se retiró al vacío. El residuo se purificó cromatográficamente sobre gel de sílice usando una mezcla de hexano/acetato de etilo como eluyente, produciendo 35,35 g (90%) del producto del título. ^{1}H RMN (400 MHz, DMSO-d_6): δ 2,27 (s, 3H), 2,87 (s, 3H), 3,20 (s, 3H), 3,26 (m, 2H), 3,39 (m, 2H), 3,59 (s, 3H), 9,82 (s, 1H). GC-MS (API-ES) calculado para $C_{10}H_{17}N_3O_2$: 211,13, encontrado ($M+H^+$): 212,1 m/z.

Ejemplo B(58): 2-{4[2-(2-Ciclopentil-5-([1-(2-fluoroetil)-3,5-dimetil-1H-pirazol-4-il]metil}4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil]-2-fluorofenil}2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo B(43) sustituyendo 1-(2-fluoroetil)-3,5-dimetil-1H-pirazol-4-carbaldehído (Etapa 2, mostrada a continuación) en lugar de 1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-carbaldehído y omitiendo la trietilamina. El producto se purificó por cromatografía sobre gel de sílice sobre un sistema Biotage. Rendimiento: 843 mg (59%). ^{1}H RMN (400MHz, DMSO-d_6): δ 1,30-1,62 (m, 8 H), 1,70 (s, 6 H), 1,84 (m, 2 H), 2,05 (s, 3 H), 2,13 (s, 3 H), 2,27 (m, 1H), 2,54 (m, 3 H), 2,68 (d, J = 19,8 Hz, 1H), 3,14 (d, J = 14,3 Hz, 1H), 3,23 (d, J = 14,3 Hz, 1H), 4,15 (d, J = 27,4 Hz, 2 H), 4,61 (d, J = 47,3 Hz, 2 H), 6,94 (d, J = 8,0, Hz, 1H), 7,05 (d, J = 11,5 Hz, 1H), 7,34 (t, J = 8,0 Hz, 1H), 10,67 (s, 1H). LC-MS (APCI) calculado para $C_{30}H_{37}F_2N_3O_3$: 525,28, encontrado ($M+H^+$): 526,30 m/z.

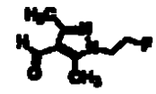
Etapa 1: 1-(2-Fluoroetil)-3,5-dimetil-1H-pirazol

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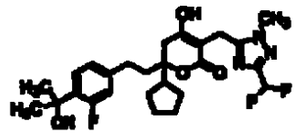
A una suspensión de hidruro sódico (1,37 mol, 60% en aceite) en DMF (350 ml) se le añadió 3,5-dimetil-1H-pirazol (120 g, 1,25 mol). Después de esto, la mezcla de reacción se agitó durante 1 h a temperatura ambiente y se trató con 1-bromo-2-fluoroetano (175 g, 1,37 mol) en DMF (200 ml). La mezcla de reacción se dejó en agitación durante una noche, se diluyó con agua (2 l) y el producto se extrajo con acetato de etilo (3 x 300 ml). Los extractos orgánicos combinados se lavaron con agua (1 L), se secaron con sulfato sódico y se evaporaron. El residuo líquido (120 g) se cromatografió sobre un aparto "Biotage" con gel de sílice usando acetato de etilo/hexano (1:5) como eluyente (R_f = 0,3) para dar 88 g (49,7%) del producto del título.

Etapa 2: 1-(2-Fluoroetil)-3,5-dimetil-1H-pirazol-4-carbaldehído



A DMF (56 g, 0,75 mol) se le añadió $POCl_3$ (74,55 ml, 0,8 mol) a 0 °C. Después de 30 minutos, al reactivo de Vilsmaier formado se le añadió 1-(2-fluoroetil)-3,5-dimetil-1H-pirazol (88 g, 0,62 mol) y la mezcla de reacción se calentó durante 16 h a 80 °C. La mezcla de reacción se diluyó con diclorometano (400 ml) y se trató con carbonato potásico (600 g) en agua (2 l) a 0 °C. La capa orgánica se separó, se pasó a través de gel de sílice (10 x 10 cm) y se evaporó. El residuo líquido se cristalizó en una mezcla de hexano (100 ml) y éter (200 ml), se separó por filtración y se secó al vacío usando una bomba de aceite para dar 26,3 g (24,9%) del producto del título. Se obtuvo satisfactoriamente el análisis de C, H, N. ^{1}H RMN (400 MHz, DMSO-d_6): δ 2,33 (s, 3H), 2,48 (s, 3H), 4,36 (dt, J = 28 Hz, J = 5 Hz, 2H), 4,74 (dt, J = 44 Hz, J = 5 Hz, 2H), 9,85 (s, 1H). GC-MS calculado para $C_8H_{11}FN_2O$: 170,09, encontrado (M^+): 170 m/z.

Ejemplo B(59): 2-{4[2-(2-Ciclopentil-5-([3-(difluorometil)-1-metil-1H-1,2,4-triazol-5-il]metil)-4-hidroxi-6-oxo3,6-dihidro-2H-piran-2-il)etil]-2-fluorofenil}-2-metilpropanonitrilo

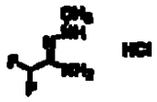


El compuesto del título se preparó de una forma análoga al ejemplo B(43) susti-

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tuyendo 3-(difluorometil)-1-metil-1H-1,2,4-triazol-5-carbaldehído (Etapa 3, mostrada a continuación) en lugar de 1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-carbaldehído y omitiendo la trietilamina. El producto se purificó por cromatografía sobre gel de sílice sobre un sistema Biotage. Rendimiento: 335 mg (24%). ^{1}H RMN (400MHz, DMSO-d6): δ 1,30-1,70 (m, 14 H), 1,91 (m, 2 H), 2,27 (m, 1H), 2,65 (m, 4 H), 3,62 (m, 2 H), 3,85 (s, 3 H),5,70 (t, J = 28 Hz, 1H), 6,99-7,08 (m, 2 H), 7,33 (t, J = 8,3 Hz, 1H). LC-MS (APCI) calculado para $C_{27}H_{31}F_3N_4O_3$: 516,23, encontrado ($M+H^+$): 517,30 m/z.

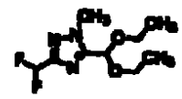
Etapa 1:Hidrocloruro de 2,2-difluoro-N'-metiletanohidrazonamida



Una corriente de amoniaco seco se pasó a través de una solución de cloruro de difluoroacetilo (157 g, 1,37 mol) en éter (1,7 L) enfriada a -5 °C con el fin de obtener un medio alcalino. La mezcla de reacción después se filtró a través de una capa de gel de sílice de 4 cm, eluyendo con éter (~2,5 l). El éter se evaporó, produciendo 111,4 g (85,5%) de 2,2-difluoroacetamida en forma de un sólido cristalino. La 2,2-difluoroacetamida (111,4 g, 1,172 mol) se mezcló con refrigeración en hielo con pentóxido de fósforo (183 g, 1,289 mol) en un matraz de 2 litros. El matraz se equipó con un condensador de reflujo y se calentó a 195 °C en un baño de aceite, usando un purgador enfriado con una mezcla hielo seco/acetona para recoger 82,8 g (1,075 mol, 91,7%) de 2,2-difluoroacetonitrilo. El 2,2-difluoroacetonitrilo resultante se enfrió a -78 °C y se añadió a una solución de metanol (44,5 ml, 1,1 mol) en éter (400 ml) enfriada a -78 °C. La mezcla se añadió lentamente con agitación a una solución de HCl (1,183 mol) en éter enfriada con hielo seco/acetona y la mezcla se mantuvo a -78 °C durante 2 h, después a -20 °C durante 24 h y después de esto a 0 °C durante 24 h. Los cristales precipitados se separaron por filtración, se lavaron con éter (2 x 500 ml) y se secaron al vacío para dar 93,5 g (59,8%) de hidrocloruro de 2,2-difluoroethanimidoato de metilo. Se añadió metilhidrazina (34,5 ml, 0,649 mol) en una atmósfera de Ar a una solución de hidrocloruro de 2,2-difluoroethanimidoato de metilo (93,5 g, 0,6425 mol) en metanol (300 ml) y la mezcla se agitó a temperatura ambiente durante 4 días. La mezcla de reacción después se diluyó con acetato de etilo, causando la cristalización parcial de una sal hidrocloruro. Los cristales (12 g) se separaron por filtración y las aguas madre se evaporaron para dar una cantidad adicional de producto. El rendimiento combinado de l hidrocloruro de 2,2-difluoro-N-metiletanohidrazonamida en bruto fue de 104,9 g (0,6208 mol, rendimiento de 96,6%). Se encontró que el compuesto tenía un % de pu-

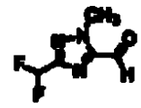
reza de área por LC/MS de 83% y se usó sin purificación adicional.

Etapa 2: 5-(Dietoximetil)-3-(difluorometil)-1-metil-1H-1,2,4-triazol



Una solución de dietoxiacetonitrilo (75 g, 0,579 mol) en metanol (210 ml) se añadió a temperatura ambiente a una solución de metóxido sódico (28,3 g, 0,522 mol) en metanol (450 ml). La mezcla se agitó durante una noche y después el metanol se evaporó. El residuo se diluyó con diclorometano (200 ml) y agua (300 ml). La capa orgánica se separó y la capa acuosa se extrajo con diclorometano (2 x 150 ml). La capa orgánica combinada se secó sobre Na_2SO_4 y se evaporó para dar 83 g de 2,2-dietoxiacetimidato de metilo en bruto (~90% de rendimiento). Una solución de 2,2-dietoxiacetimidato de metilo preparado anteriormente (0,6208 mol, 125,1 g, pureza de 80%) en metanol (300 ml) se añadió a una solución de hidrocloruro de 2,2-difluoro-N-metiletanohidrazonamida (0,6208 mol, obtenido en la Etapa 1) en metanol (700 ml). Se añadió acetato sódico anhidro (61,1 g, 0,745 mol) y la mezcla se agitó a 30 °C durante 3 días. Después, la mezcla de reacción se evaporó y el residuo se sometió a cromatografía (acetato de etilo/hexano 1:4 → 1:1) sobre una columna de gel de sílice, seguido de destilación al vacío para dar 47,6 g (32,6%) de 5-(dietoximetil)-3-(difluorometil)-1-metil-1H-1,2,4-triazol.

Etapa 3: 3-(Difluorometil)-1-metil-1H-1,2,4-triazol-5-carbaldehído

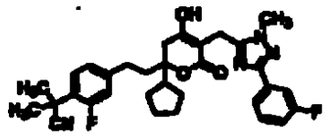


Se añadió agua (190 ml) a 5-(dietoximetil)-3-(difluorometil)-1-metil-1H-1,2,4-triazol (47,6 g, 0,2024 mol, de la etapa 2) y la mezcla se desgasificó. Después se añadió HCl concentrado (73 ml, 0,81 mol, 11,1 M) y la mezcla se agitó a 55-60 °C durante 24 h. Después de esto, la mezcla de reacción se evaporó y el residuo se evaporó repetidamente (8-10 times) con THF hasta que se retiraron completamente el agua y el HCl. El residuo final se destiló al vacío para dar el producto del título bruto (p.e. 46-50 °C a 0,04 mm Hg), que contenía, de acuerdo con los datos de LC-MS, 7% de un producto secundario de dimerización. La purificación adicional sobre gel de sílice (acetato de etilo/hexano, 1:3) produjo 18,37 g (56,3%) de 3-(difluorometil)-1-metil-1H-1,2,4-triazol-5-carbaldehído. Se obtuvo satisfactoriamente el análisis de C, H, N. ^{1}H RMN (400 MHz,

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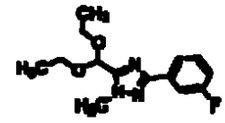
$CDCl_3$): δ 4,25 (s, 3H), 6,74 (t, J = 56 Hz, 1H), 10,01 (s, 1H). LC/MS (API-ES) calculado para $C_5H_5F_2N_3O$: 161,04, encontrado ($M+H^+$): 162,1; ($M+18+H^+$): 180,1 m/z.

Ejemplo B(60): 2-{4-[2-(2-Ciclopentil-5-{[3-(3-fluorofenil)-1-metil-1H-1,2,4-triazol-5-il]metil}-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il)etil]-2-fluorofenil}2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo B(43) sustituyendo hidrocloruro de 3-(3-fluorofenil)-1-metil-1H-1,2,4-triazol-5-carbaldehído dihidrato (Etapa 2, mostrada a continuación) en lugar de 1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-carbaldehído. El producto se purificó por cromatografía sobre gel de sílice sobre un sistema Biotage. Rendimiento: 260 mg (17%). ^{1}H RMN (400MHz, DMSO-d_6): δ 1,38-1,70 (m, 14 H), 2,04 (m, 2 H), 2,42 (m, 1H), 2,63 (m, 3 H), 2,75 (d, J = 19,8 Hz, 1H), 3,65 (d, J = 15,8 Hz, 1H), 3,74 (d, J = 15,8 Hz, 1H), 3,89 (s, 3 H), 6,99 (d, J-7,8 Hz, 1H), 7,09-7,20 (m, 3 H), 7,35 (m, 1H), 7,48 (d, J = 9,8 Hz, 1H), 7,64 (d, J = 8,1Hz, 1H), 11,18 (s, 1H). LC-MS
(APCI) calculado para $C_{22}H_{24}F_2N_4O_3$: 560,26, encontrado ($M+H^+$): 561,30 m/z.

Etapa 1: 5-(Dietoximetil)-3-(3-fluorofenil)-1-metil-1H-1,2,4-triazol

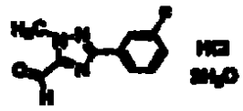


Se añadió MeONa (2,35 g, 41 mmol) a una solución agitada de 3-fluorobenzonitrilo (50,0 g, 413 mmol) en metanol (300 ml). La mezcla se agitó a temperatura ambiente durante 3 días y se concentró al vacío. El residuo se disolvió en éter (300 ml), se lavó con agua (2 x 150 ml) y salmuera (150 ml), se secó con Na_2SO_4 y se concentró al vacío para producir 62,8 g (99%) of 3-fluorobencenocarboximidoato de metilo. Se añadió metilhidrazina (21,8 ml, 410 mmol) a una solución agitada de 3-fluorobencenocarboximidoato de metilo (62,8 9, 410 mmol) en THF (350 ml). La mezcla se agitó a temperatura ambiente durante 3 días. Después se añadieron 2,2-dietoxiethanimidoato de metilo (66,1 g, 410 mmol) y ácido acético (37,5 ml, 656 mmol). La mezcla se agitó durante 24 h. La reacción se diluyó con CH_2Cl_2 (500 ml) y el precipitado formados e retiró por filtración. El filtrado se lavó con ácido cítrico al 10% (2 x 200

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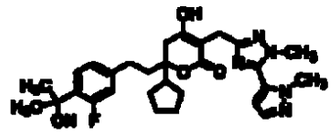
ml), agua (300 ml) y salmuera (200 ml), se secó con Na_2SO_4, y se concentró al vacío. El residuo se sometió a cromatografía ultrarrápida sobre gel de sílice usando MeOH al 1%/$CHCl_3$ como eluyente para dar 24,0 g (21 %) del producto del título.

Etapa 2: Hidrocloruro de 3-(3-fluorofenil)-1-metil-1H-1,2,4-triazol-5-carbaldehído dihidrato



Una solución de 5-(dietoximetil)-3-(3-fluorofenil)-1-metil-1H-1,2,4-triazol (24,0 g, 86 mmol) en HCl 4 M (86 ml) se agitó a 60 °C durante 2 h. La mezcla se concentró al vacío y el residuo se recristalizó en una mezcla de MeOH/Et_2O (1:1). El solvato resultante se disolvió en agua/THF (1:2) y se concentró al vacío a sequedad para producir 11,33 g (47%) del producto del título. Se obtuvo satisfactoriamente el análisis de C, H, N. ^{1}H RMN (400 MHz, D_2O+TFA): δ 4,16 (s, 3H), 8,47 (s, 1H), 7,42 (m, 1H), 7,82 (m, 1H), 7,70 (m, 1H), 7,77 (m, 1H). LC/MS (API-ES) calculado para $C_{10}H_8FN_3O$: 205,07, encontrado ($M+H^+$): 206,0; ($M+18+H^+$): 224,0 m/z.

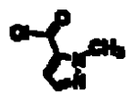
Ejemplo B(61): 2-{4[2-(2-Ciclopentil-4-hidroxi-5-{[1-metil-5-(1-metil-1H-pirazol-5 il)-1H-1,2,4-triazol-3-il]metil}-6-oxo-3,6-dihidro-2H-piran-2-il)etil]-2-fluorofenil}-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo B(43) sustituyendo 1-metil-5-(1-metil-1H pirazol-5-il)-1H-1,2,4-triazol-3-carbaldehído (Etapa 3, mostrada a continuación) en lugar de 1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-carbaldehído y omitiendo la trietilamina. E producto se purificó por cromatografía sobre gel de sílice sobre un sistema Biotage. Rendimiento: 67 mg (4%). ^{1}H RMN (400MHz, DMSO-d_6): δ 1,36-1,70 (m, 14 H), 2,07 (m, 2 H), 2,34 (m, 2 H), 2,63 (m, 3 H), 3,46-3,57 (m, 2 H), 3,74 (s, 3 H), 3,84 (s, 3 H), 6,76(s, 1H), 7,01-7,22 (m, 3 H), 7,59 (s, 1H). LC-MS (APCI) calculado para $C_{30}H_{38}FN_5O_3$: 546,28, encontrado ($M+H^+$): 547,30 m/z.

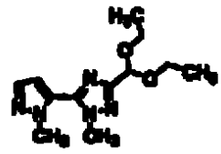
Etapa 1: Cloruro de 1-metil-1H-pirazol-5-carbonilo

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A una solución agitada de 1-metil-1H-pirazol (77,0 g 0,916 mol) en éter absoluto (960 ml) en una atmósfera de argón se le añadió gota a gota una solución 1,6 M de n-BuLi en hexano (600 ml, 0,96 mol) -40 °C durante un periodo de 2 h. La mezcla de reacción se agitó a esta temperatura durante 1 h más y después se sifonó en una mezcla de dióxido de carbono sólido con éter. Después de calentar a temperatura ambiente, la masa resultante se trató con agua (1,5 l), la capa acuosa se separó, se lavó con éter (500 ml), se concentró hasta la mitad del volumen a presión reducida en un evaporador rotatorio, se enfrió a 2-3 °C y se acidificó mientras se agitaba con HCl concentrado a pH = 3. El precipitado resultante se separó por filtración, se lavó con agua enfriada con hielo (25 ml), se secó primero al aire abierto y después en un desecador al vacío sobre P205 para dar 88,5 g (76%) de ácido 1-metil-1H-pirazol-5-carboxílico en forma de un polvo blanco. Al cloruro de tionilo (650 ml) se le añadió en porciones ácido 1-metil-1H-pirazol-5-carboxílico (86,5 g, 0,67 mol) durante un periodo de 35 minutos, de tal forma que cada porción se consumió antes de la adición de la siguiente. Después de esto, la mezcla de reacción se calentó a reflujo durante 4,5 h. El exceso de cloruro de tionilo se retiró al vacío a una temperatura del baño inferior a 35 °C. El residuo se sometió a destilación fraccionada al vacío a través de una columna Vigreux de 15 cm. Se recogió una fracción que hervía a 71-72 °C a 15-16 mm Hg para obtener el producto del título (49,0 g,51 %) en forma de un líquido incoloro.

Etapa 2: 3-(Dietoximetil)-1-metil-5-(1-metil-1H-pirazol-5-il)-1H-1,2,4-triazol

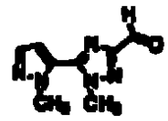


A una solución agitada de dietoxiacetonitrilo (60 g, 0,465 mol) en metanol absoluto (150 ml) en una atmósfera de argón se le añadió una solución de acetato sódico (2,5 g; 0,047 mol) en metanol absoluto (20 ml) y la mezcla de reacción se agitó a temperatura ambiente hasta que el nitrilo desapareció completamente (70-75 h). La reacción se controló por ^{1}H RMN. La mezcla de reacción se trató, mientras se agitaba, con CO_2 hasta que cesó la formación del precipitado de carbonato sódico. La capa se filtró y se lavó con metanol (50 ml). El filtrado se evaporó en un evaporador rotatorio a una temperatura del baño de 30 °C. El líquido resultante se disolvió en éter (250 ml), se

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filtró para retirar las sales inorgánicas restantes y se evaporó de nuevo para dar el 2,2-dietoxiethanimidoato de metilo bruto (71,0 g, 95%). Se destiló al vacío a través de una columna Vigreux de 15 cm, produciendo 56,2 g (75%) de 2,2-dietoxiethanimidoato de metilo (p.e. 77-78 °C a 20-22 mm Hg) con una pureza mayor de 95% según indicó el análisis por ^{1}H RMN. A una solución del 2,2-dietoxiethanimidoato de metilo (52,1 g, 0,321 mol) y trietilamina (49 ml, 0,353 mol) en THF absoluto (300 ml) se le añadió gota a gota una solución de cloruro de 1-metil-1H-pirazol-5-carbonilo (46,5 g, 0,321 mol, de la etapa 1) en THF absoluto (150 ml) en una atmósfera de argón a 0-5 °C durante un periodo de 2 h. La mezcla de reacción se agitó durante una noche a temperatura ambiente. El residuo formado se retiró por filtración y el filtrado se evaporó en un evaporador rotatorio para dar (1Z)-2,2-Dietoxi-N-[(1-metil-1H-pirazol-5-il)carbonil]etanimidoato de metilo (90 g) en forma de una masa viscosa, que se usó en la siguiente etapa sin purificación adicional. Los 90 g del producto éster de imidato N-acilado bruto obtenidos en la etapa previa se disolvieron en diclorometano absoluto (450 ml) y se trataron con metilhidrazina (17,1 ml, 0,321 mol) con agitación durante un periodo de 10 min. La mezcla de reacción se agitó a temperatura ambiente durante 3 h, se lavó con agua (3 x 300 ml) y se secó con sulfato sódico anhidro. El disolvente se retiró al vacío en un evaporador rotatorio y el residuo (56,5 g) se purificó cromatográficamente sobre gel de sílice usando hexano/acetato de etilo (1:2) como eluyente. El disolvente se evaporó para dar 40,1 g (47% basado en el cloruro de 1-metil-1H-pirazol-5-carbonilo) del producto del título bruto.

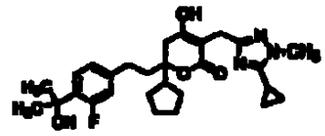
Etapa 3: 1-Metil-5-(1-metil-1H-pirazol-5-il)-1H-1,2,4-triazol-3-carbaldehído



A una solución 4 N de HCl (185 ml, 0,74 mol) se le añadió 3-(dietoximetil)-1-metil-5-(1-metil-1H-pirazol-5-il)-1H-1,2,4-triazol (40,1 g, 0,151 mol) y la mezcla de reacción se dejó en agitación durante una noche. A la mezcla resultante se le añadió carbonato potásico (166 g) en porciones con agitación vigorosa y la mezcla resultante se extrajo con acetato de etilo (5 x 300 ml). La capa orgánica se secó con sulfato sódico anhidro y los disolventes se retiraron al vacío en un evaporador rotatorio. Al residuo se le añadió éter absoluto (4 x 100 ml) para dar 27,3 g (94,5%) del producto del título en forma de un polvo beige claro. Se obtuvo satisfactoriamente el análisis de C, H, N. ^{1}H RMN (400 MHz, DMSO-d_6): δ 4,04 (s, 3H), 4,08 (s, 3H), 6,96 (d, J = 2 Hz, 1H), 7,67 (d,

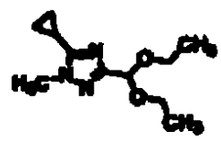
J = 2 Hz, 1H), 9,95 (s, 1H). LC/MS (API-ES) calculado para $C_8H_9N_3O$: 191,08, encontrado ($M+H^+$): 192,0 m/z.

Ejemplo B(62): 2-[4(2-{2-Ciclopentil-5-[(5-ciclopropil-1-metil-1H-1,2,4-triazol-3-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo B(43) sustituyendo 5-ciclopropil-1-metil-1H-[1,2,4]triazol-3-carbaldehído (Etapa 2, mostrada a continuación) en lugar de 1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-carbaldehído y omitiendo la trietilamina. El producto se purificó por cromatografía sobre gel de sílice sobre un sistema Biotage. Rendimiento: 326 mg (23%). ^{1}H RMN (400MHz, DMSO-d_6): δ 0,70 (m, 2 H), 0,90 (m, 2 H), 1,36-1,71 (m, 14 H), 1,97-2,12 (m, 3 H), 2,39 (m, 1H), 2,52 (d, J = 15,8 Hz, 1H), 2,63 (m, 2 H), 2,72 (d, J = 15,8 Hz, 1H), 3,37 (d, J = 15,8 Hz, 1H), 3,47 (d, J = 15,8 Hz, 1H), 3,65 (s, 3 H), 7,10 (m, 2 H), 7,37 (t, J = 8,3 Hz, 1H), 10,70 (s, 1H). LC-MS (APCI) calculado para $C_{29}H_{33}FN_4O_3$: 508,27, encontrado (M+H): 507,30 m/z.

Etapa 1: 5-Ciclopropil-3-dietoximetil-1-metil-1H-[1,2,4]triazol



Se cargaron ciclopropanocarbonitrilo (100 g, 1,49 mol), metanol (59,7 g, 76 ml, 1,86 mol) y éter dietílico (184 ml) en un matraz de 2 litros y de tres bocas. La mezcla se enfrió a -10 °C mientras se agitaba y se burbujeó HCl (g) (232 g, 6,36 mol) a través de la solución de mezcla de tal forma que la temperatura interna se mantuvo por debajo de -5 °C. Después de completarse la adición de gas, la mezcla se agitó durante 1,5 h a -10 °C. Se añadió lentamente éter (685 ml) durante un periodo de 1 h, continuando para mantener la temperatura por debajo de 0 °C. Los sólidos resultantes se filtraron y se aclararon con éter dietílico (3 x 300 ml). Los sólidos se secaron al vacío, produciendo 181,5 g (89,8 % de rendimiento) de hidrocloruro de ciclopropanocarboximidoato de metilo. P.f.: 112-114 °C

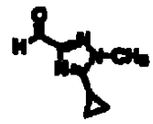
En un matraz de 2 litros y de tres bocas, se trató una solución de dietoxiacetonitrilo

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(125 g , 968 mmol) en metanol (300 ml, anhidros) con una solución al 25% en peso de metóxido sódico (21,0 g, 389 mmol) en metanol, produciendo una reacción ligeramente exotérmica. Después de enfriar, la mezcla se agitó a temperatura ambiente durante 15 h. Después de completarse la reacción, el disolvente se evaporó lentamente al vacío. El residuo de color pardo restante se solvató con éter dietílico (1 l) y después se lavó con agua (3 x 500 ml), seguido de salmuera (1 x 200 ml). La capa orgánica se secó usando sulfato de magnesio, las sales se filtraron y el disolvente se evaporó cuidadosamente al vacío para producir 132 g (85 % de rendimiento) of 2,2-dietoxiethanimidoato de metilo en forma de un líquido incoloro.

Se disolvió 2,2-dietoxietanimidoato de metilo (39,0 g, 242 mmol) en tetrahidrofurano (345 ml), se mezcló con metilhidrazina (11,1 g, 242 mmol) y después la mezcla se agitó a temperatura ambiente durante 5 h, momento en el que el análisis por LC/MS confirmó la formación del intermedio de amidrazona. Se añadió hidrocloruro de ciclopropanocarboximidoato de metilo (32,8 g, 242 mmol) a la mezcla de reacción, dando como resultado una suspensión. Se añadió lentamente ácido acético (21,8 g, 363 mmol) a la suspensión y la reacción exotérmica resultante se controló con un baño de refrigeración. Después de completarse la adición, la mezcla de reacción se agitó a temperatura ambiente durante una noche. Después de que el análisis por LC/MS indicara que los reactivos de partida se habían consumido, la mezcla se diluyó con diclorometano (500 ml) y se agitó durante 1 h. Los sólidos se filtraron, se aclararon con diclorometano (3 x 200 ml) y el filtrado se concentró al vacío. El aceite restante se purificó por cromatografía en columna sobre gel de sílice (fase móvil: acetato de etilo y después con metanol al 1, 3,5 y 10%, consecutivamente). Las fracciones que contenían el producto se enfriaron y el disolvente se evaporó al vacío. Después de secar adicionalmente a alto vacío, se obtuvieron 27,4 g del acetal del título en forma de un aceite que contenía 12,4% en peso de etilo como una impureza.

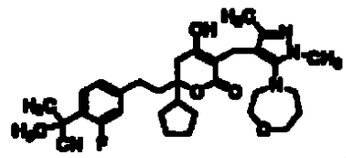
Etapa 2: 5-Ciclopropil-1-metil-1H-[1,2,4]triazol-3-carbaldehído



En un matraz de fondo redondo de 2 litros que contenía el 5-ciclopropil-3-(dietoximetil)-1-metil-1H-1,2,4-triazol bruto de la etapa 2, se añadió una solución de HCl 2 N (125 ml) y la reacción se dejó en agitación a temperatura ambiente durante 23 h, momento en el que el análisis por LC/MS confirmó la formación del aldehído. La mez-

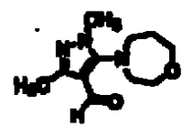
cia después se trató con hidróxido sódico sólido hasta que se obtuvo un valor de pH de 13. La mezcla acuosa se extrajo con diclorometano (3 x 150 ml) y las capas orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y el disolvente se evaporó al vacío. El material bruto se destiló por destilación de Kugel-Rhor a 135 °C-146 °C para producir 11,4 g (61,9 %) del producto del título en forma de un aceite de color amarillo. Este material contenía un 4,8% en peso del producto secundario auto-condensado, 3,5-diciclopropil-l-metil-1H-1,2,4-triazol, según indicó el análisis por ^{1}H RMN. ^{1}H RMN (300 MHz, DMSO-d_6): δ 0,96 (m, 2H), 1,10 (m, 2H), 2,22 (m, 1H), 4,00 (s, 3H), 9,78 (s, 1H). LC/MS (APCI) calculado para $C_7H_8N_3O$: 151,07, encontrado ($M+H^+$): 152,1 m/z.

Ejemplo B(63): 2-{4-[2-(2-Ciclopentil-5-{[1,3-dimetil-5-(1,4-oxazepan-4-il)-1H-pirazol-4 il]metil}-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2 il)etil]-2-fluorofenil}-2-metilpropanonitrilo



El compuesto del título se preparó de una forma análoga al ejemplo B(43) sustituyendo 1,3-dimetil-5-(1,4-oxazepan-4-il)-1H-pirazol-4-carbaldehído (etapa 1, mostrada a continuación) en lugar de 1-metil-3-(6-metilpiridin-2-il)-1H-1,2,4-triazol-5-carbaldehído y omitiendo la trietilamina. El producto se purificó por cromatografía sobre gel de sílice en un sistema Biotage. Rendimiento: 553 mg (35 %). ^{1}H RMN (400MHz, DMSO-d_6): δ 1,32-1,64 (m, 8 H), 1,70 (s, 6 H), 1,82 (m, 2 H), 1,89 (m, 2 H), 1,94 (s, 3 H), 2,32 (m, 1H), 2,57 (m, 3 H), 2,68 (d, J = 17,6 Hz, 1H), 3,17-3,27 (m, 6 H), 3,52 (s, 3 H), 3,64 (m, 2 H), 3,78 (t, J = 5,8 Hz, 2 H), 6,99 (d, J = 8,1Hz, 1H), 7,08 (d, J = 13,1Hz, 1H), 7,35 (t, J = 8,6 Hz, 1H), 10,69 (s, 1H). LC-MS (APCI) calculado para $C_{33}H_{43}FN_4O_4$: 578,33, encontrado ($M+H^+$): 579,40 m/z.

Etapa 2: 1,3-Dimetil-5-(1,4-oxazepan-4-il)-1H-pirazol-4-carbaldehído

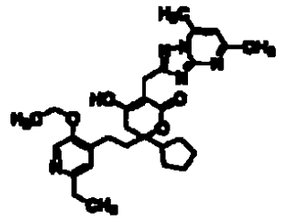


Se añadió hidrocloruro de homomorfolina (26,2 g, 200 mol) a una mezcla de 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído (21,68 g, 0,1368 mol, Ejemplo B(45), Etapa 2), HMPA (30 ml), agua (50 ml) y carbonato potásico (59 g, 0,6 mol) con agitación

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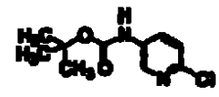
constante y a temperatura ambiente. La mezcla de reacción se calentó a 80 °C durante 50 h, se diluyó con agua y se extrajo con acetato de etilo (3 x 100 ml). Los extractos orgánicos se lavaron con agua hasta un pH ligeramente alcalino y se secaron con sulfato sódico. El producto se purificó cromatográficamente usando una mezcla de hexano/acetato de etilo como eluyente para producir el producto del título (18,7 g, 61%). Se obtuvo satisfactoriamente el análisis de C, H, N. ^{1}H RMN (400 MHz, DMSO-d_6): δ 1,91 (m, 2H), 2,27 (s, 3H), 3,33 (m, 4H, solapado con pico de H_2O), 3,62 (s, 3H), 3,72 (m, 2H), 3,81 (m, 2H), 9,83 (s, 1H). LC/MS (API-ES) calculado para $C_{11}H_{17}N_3O_2$: 223,13, encontrado ($M+H^+$): 224,1 m/z.

Ejemplo B(64): 6-Ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etoxi-2- etilpiridin-4-il)etil] 4-hidroxi-6,6-dihidro-2H-piran-2-ona



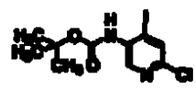
El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 6-ciclopentil-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]dihidro-2H-piran-2,4(3H)-diona de la etapa 8 mostrada a continuación en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,19 (t, J = 7,6 Hz, 3 H), 1,31 (t, J = 6,8 Hz, 3 H), 1,40-1,78 (m a, 8 H), 2,03-217 (m, 2 H), 2,48-2,72 (m, 12 H), 2,85 (d, J = 17,4 Hz, 1H), 3,76 (d, J = 16,4 Hz, 1H), 3,87 (d, J = 16,2 Hz, 1H), 4,08 (m, 2 H), 7,09 (m, 2 H), 8,13 (s, 1H), 10,96 (s, 1H). MS (ESI): 520,20 $(M+H)^+$

Etapa 1: Éster terc-butílico del ácido (6-cloro-piridin-3-il)-carbámico



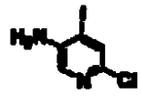
Se añadió dicarbonato de di-terc-butilo (41 g, 0,19 mol) a una solución de 5-amino-2-cloropiridina (20 g, 0,16 mol) disuelta en 1,4-dioxano (120 ml). La mezcla de reacción se calentó a reflujo durante 16 horas. La reacción se enfrió a temperatura ambiente, se vertió en H_2O y se extrajo con éter. Los extractos orgánicos se secaron sobre Na_2SO_4 y se concentraron hasta un residuo. La trituración con hexanos dio el producto en forma de un sólido castaño (31 g, 85%). ^{1}H RMN (400MHz, $CDCl_3$): δ 1,52 (s, 9 H), 6,58 (s, 1H), 7,26 (d, J = 8,6 Hz, 1H), 7,96 (m, 1H), 8,23 (d, J = 2,8 Hz, 1H).

Etapa 2: Éster terc-butílico del ácido (6-cloro-4-yodo-piridin-3 il)-carbámico



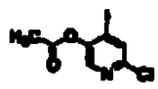
Se añadió gota a gota n-BuLi (52,4 ml, 0,12 mol, solución 2,5 M en hexanos) durante 30 minutos a una solución enfriada a -78 °C de éster terc-butílico del ácido (6-cloro-piridin-3-il)-carbámico (10,0 g, 43,7 mmol) y TMEDA (19,8 ml, 0,13 mol) disueltos en éter. La solución se calentó a -10 °C, se agitó durante 2 horas y después se enfrió de nuevo a -78 °C. Se añadió una solución de yodo (22,75 9, 90 mmol) en éter (100 ml) mediante un embudo de adición y la reacción se calentó a temperatura ambiente y se agitó durante 16 horas. La reacción se interrumpió con NH_4Cl saturado y se añadió tiosulfito sódico. La mezcla se agitó durante 30 minutos y después se extrajo con éter. Los extractos orgánicos se lavaron con tiosulfito sódico, se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por cromatografía sobre gel de sílice (EtOAc al 0%-15% en hexanos) dio el producto (8,6 g,56%). ^1H RMN (300 MHz, $CDCl_3$): δ 1,52 (s, 9 H), 6,58 (s, 1H), 7,26 (d, J = 8,6 Hz, 1H), 7,96 (m, 1H), 8,23 (d, J = 2,8 Hz, 1H).

Etapa 3: 6-Cloro-4-yodo-piridin-3-ilamina



Una solución de éster terc-butílico del ácido (6-cloro-4-yodo-piridin-3-il)-carbámico (8,6 g, 24,3 mmol) disuelto en CH_2Cl_2 se trató con HCl 4 N/dioxano (100 ml) y se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con CH_2Cl_2 y se lavó con NaOH 2 N. La capa orgánica se secó sobre $MgSO_4$ y se concentró para dar el producto en forma de un sólido (6,2 g, 100%).

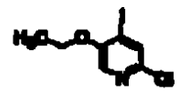
Etapa 4: 6-Cloro-4-yodo-piridin-3-il éster del ácido acético



Se añadió lentamente eterato de dietilo de trifluoruro de boro (6,2 ml, 48,9 mmol) a una solución enfriada a -15°C de 6-cloro-4-yodo-piridin-3-ilamina (5,82 g, 22,9 mmol) disuelta en DME (36 ml) y CH_2Cl_2 (12 ml). Se añadió lentamente nitrito de terc-butilo (3,6 ml, 27,6 mmol) manteniendo la temperatura por debajo de -5 °C. La reacción se agitó a -10 °C durante 25 minutos y después a 0 °C durante 20 minutos. La mezcla

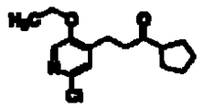
se diluyó con pentanos (100 ml) y la sal tetrafluoroborato de diazonio se recogió por filtración. La sal se disolvió inmediatamente por disolución en anhídrido acético (20 ml) y se calentó a 95 °C durante 2 horas. La reacción se enfrió a temperatura ambiente y se repartió entre éter dietílico y $NaHCO_3$ saturado. La capa orgánica se secó sobre $MgSO_4$ y se concentró. La purificación por cromatografía sobre gel de sílice (EtOAc al 0%-60% en hexanos) dio el producto en forma de un sólido blanco (3,34 g, 49%). ^1H RMN (300 MHz, $CDCl_3$): δ 2,40 (s, 3 H), 7,82 (s, 1H), 8,09 (s, 1H).

Etapa 5: 2-Cloro-5-etoxi-4-yodo-piridina



Una mezcla de 6-cloro-4-yodo-piridin-3-il éster del ácido acético (3,58 g, 12,1 mmol) y carbonato potásico (0,83 g, 6,0 mmol) en MeOH (20 ml) se agitó durante 90 minutos. El disolvente se retiró al vacío y el residuo se repartió entre éter y ácido cítrico 1 N. La capa orgánica se secó sobre $MgSO_4$ y se concentró para dar un sólido blanquecino (2,86 g, 95%). El sólido se disolvió en DMF (20 ml) y se trató con carbonato potásico (4,63 g, 34 mmol) seguido de yoduro de etilo (2,73 ml, 33,6 mmol). La mezcla de reacción se calentó a 60 °C durante 2 horas y después se enfrió a temperatura ambiente. La mezcla se vertió en ácido cítrico al 20% y se extrajo con éter. Los extractos de éter se lavaron con H_2O y salmuera, se secaron sobre $MgSO_4$ y se concentraron. La purificación por cromatografía sobre gel de sílice (EtOAc al 0%- 60% en hexanos) dio el compuesto en forma de un sólido blanco (3 g, 95%). ^1H RMN (300 MHz, $CDCl_3$): δ 1,51 (t, J = 7,0 Hz, 3 H), 4,17 (q, J = 7,0 Hz, 2 H), 7,74 (s, 1H), 7,81 (s, 1H).

Etapa 6: 3-(2-Cloro-5-etoxi-piridin-4-il)-1-ciclopentil-propan-1-ona

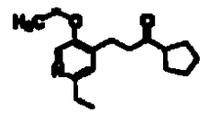


Una mezcla de 2-cloro-5-etoxi-4-yodo-piridina (1,5 g,5,3 mmol), 1-ciclopentil-2-propen-1-ol (0,83 g, 6,61 mmol), acetato sódico (0,54 g, 6,6 mmol) y acetato de paladio (II) (24 mg, 0,11 mmol) en DMAC (10 ml) se calentó a 90 °C en una atmósfera de N_2 durante 16 horas. La mezcla de reacción se repartió entre HCl 1 N y EtOAc. Las capas orgánicas se lavaron con $NaHCO_3$ saturado y salmuera, se secaron sobre $MgSO_4$ y se concentraron. La purificación por cromatografía sobre gel de sílice (EtOAc al 0%-60% en hexanos) dio el producto deseado (1,2 g,58%). ^1H RMN (300 MHz, $CDCl_3$): δ 1,44 (t,

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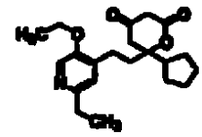
J = 7,0 Hz, 3 H), 1,55-1,87 (m, 8 H), 2,75 (m, 2 H), 2,86 (m, 3 H), 4,11 (q, J = 7,0 Hz, 2 H), 7,09 (s, 1H), 7,89 (s, 1H).

Etapa 7: 1-Ciclopentil-3-(5-etoxi-2-etil-piridin-4-il)-propan-1-ona



Una solución de 3-(2-cloro-5 etoxi-piridin-4-il)-1-ciclopentil-propan-1-ona (1,2 g, 4,3 mmol) disuelta en DMF (10 ml) se trató con carbonato potásico (0,88 g, 6,4 mmol), tetraquis(trifenilfosfina)paladio (0,12 g, 0,11 mmol) y trietilborano (4,5 ml, 4,5 mmol). La reacción se calentó a 150°C durante 2 horas. La reacción se interrumpió con HCl 1 N y después se basificó con NaOH 2 N. La mezcla se extrajo con éter y las capas orgánicas se secaron sobre $MgSO_4$ y se concentraron. La purificación por cromatografía sobre gel de sílice (EtOAc al 0%-60% en hexanos) dio el producto (0,8 g, 68%). ^1H RMN (300 MHz, $CDCl_3$): δ 1,26 (t, J = 7,6 Hz, 3 H), 1,42 (t, J = 6,9 Hz, 3 H), 1,55-1,87 (m, 8 H), 2,73 (m, 4 H), 2,86 (m, 3 H), 4,11 (q, J = 6,9 Hz, 2 H), 6,93 (s, 1H), 8,06 (s, 1H).

Etapa 8: 6-Ciclopentil-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]dihidro-2H-piran-2,4(3H)-diona

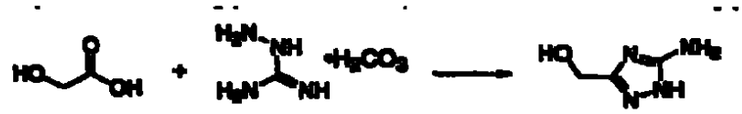


Se añadió acetoacetato de metilo (1,2 ml, 10,9 mmol) a una suspensión enfriada a -50 °C de LDA [preparada a partir de diisopropilamina (3,0 ml, 21,8 mmol) y n-BuLi (8,7 ml, 21,8 mmol) disueltos en THF (30 ml)]. La reacción se agitó durante 30 minutos y después se añadió una solución de 1-ciclopentil-3 (5 thoxi-2-etil-piridin-4-il)-propan-1-ona (1,0 g, 3,6 mmol) disuelta en THF (30 ml). La reacción se calentó a temperatura ambiente y se agitó durante 2 horas. La reacción se vertió en NaOH 1 N y se extrajo con EtOAc. Las capas orgánicas se secaron sobre $MgSO_4$ y se concentraron. El residuo se disolvió en metanol (100 ml), se trató con carbonato potásico (1,5 g, 10,9 mmol) y se calentó a reflujo en una atmósfera de N_2 durante 120 minutos. La mezcla de reacción se repartió entre H_2O e IPE. La capa acuosa se neutralizó con HCl 1 N y se extrajo con EtOAc. Las capas orgánicas se secaron sobre $MgSO_4$ y se concentraron para dar el producto (1,3 g, 99% de rendimiento). ^1H RMN (400 MHz, $CDCl_3$): δ 1,26 (t, J = 7,6 Hz, 3 H), 1,43 (t, J = 6,8 Hz, 3 H), 1,50-2,05 (m a, 9 H), 2,34 (m, 2 H), 2,62-2,77 (m, 6

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H), 3,44 (m, 2 H), 4,11 (q, J = 6,8 Hz, 2 H), 6,90 (s, 1H), 8,08 (s, 1H).

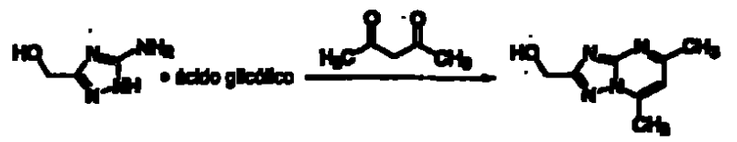
Ejemplo (C1): Preparación de la sal glicolato de (5-amino-1H-1,2,4-triazol-3-il)metanol



sal glicolato

A un matraz de 5 litros se le añadió ácido glicólico (1 l, 70% en agua, 11,51 mol). A la solución se le añadió lentamente bicarbonato de aminoguanidina (783,33 g,5,755 mol) en porciones para controlar el burbujeo significativo. Según se añaden los sólidos, la solución se enfría debido a la disolución endotérmica. La solución se calentó suavemente para mantener una temperatura interna de 25°C durante la adición. Diez minutos después de completarse la adición de bicarbonato de aminoguanidina, se añadió cuidadosamente ácido nítrico conc. (6,8 h ml). La solución se calentó a una temperatura interna de 104-108 °C (reflujo suave) durante 22 h. El calentamiento se interrumpió y la solución se dejó enfriar, con agitación. A la temperatura interna de 81°C, los sólidos empezaron a cristalizar. Después de que la temperatura interna estuviera justo por debajo de 80°C, se añadió lentamente etanol (absoluto, 375 ml) a la mezcla. Después de que la temperatura interna se hubiera enfriado a 68°C, el enfriamiento se aceleró usando un baño de hielo/agua. Después de enfriar por debajo de ta, la solución se hizo muy espesa aunque permaneció agitable en todo momento. La suspensión se agitó durante 2 h a T<10°C, después se filtró y los sólidos se agitaron con etanol (900 ml frío, después 250 ml a ta). Los sólidos se secaron durante una noche en una estufa de vacío (~25 mmHg, 45-50 °C) para proporcionar 815,80 g (75%) de (5-amino-1H-1,2,4-triazol-3-il)metanol en forma de la sal glicolato. ^{1}H (300 MHz, d_6-DMSO): 3,90 (s, 2), 4,24 (s, 2).

Ejemplo (C2): Preparación of (5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2 il)metanol



Un reactor de 10 l se cargó HOAc (4,7 l), 2,4-pentanodiona (543 ml,5,29 mol) y la sal glicolato de (5-amino-1H-1,2,4-triazol-3-il)metanol (944 g, 4,96 mol). La mezcla se calentó a 100°C hasta que la solución fue homogénea. Después de alcanzar los 100°C,

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la solución era casi homogénea. El tiempo a 100°C debería ser de 15-30 min. Después de este tiempo, si la solución permanece turbia debería interrumpirse el calentamiento. La solución resultante se enfrió a temperatura ambiente y se añadió MTBE (16 l) y la mezcla se agitó durante 30 min. La mezcla se filtró a través de un Buchner de 14" (35,56 cm), se aclaró con MTBE (7 l) y se secó en un horno de vacío durante una noche a 50°C para proporcionar 518 g (59%) de (5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metanol en forma de un sólido blanco. El filtrado contenía producto significativo, por lo que se aisló un segundo cultivo cargando los filtrados de MTBE en un reactor de 22 l y enfriando a 0°C. Se añadió MTBE (8 l) y se agitó durante 2 horas. La suspensión resultante se filtró y se secó para producir 173,7 g adicionales (20%) de (5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metanol en forma de un sólido gris. Se continuó con ambos cultivos. ^{1}H RMN (300 MHz, d_6-DMSO): 2,57 (s, 3), 2,71 (d, 3, J = 0,8), 4,63 (d desigual, 2, J = 5,7),5,49 (t, 1, J = 6,2), 7,13 (d, 1, J = 0,8).

Ejemplo (C3): Preparación de 5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído



Un reactor de 10 l se cargó secuencialmente CH_2Cl_2 (5,1 l), (5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metanol (680 g, 3,816 mol) y diacetato de yodobenceno (1352 g, 4,197 mol). Según se disuelve el diacetato de yodobenceno, hay una endotermia significativa (típicamente por debajo de 15-16°C). La camisa se ajustó a 23°C. La mezcla se calentó a temperatura ambiente y se añadió en una sola carga de Tempo (2,2,6,6-tetrametil-l-pipendiniloxd, radical libre, 43,75 g, 0,28 mol). La reacción se agitó hasta que sólo permanecía el 5% del alcohol de partida por HPLC. Una vez que se valoró que quedaba menos de aproximadamente ~5% de material de partida, se comenzó a observar el producto sobre-oxidado. Permitiendo que la reacción transcurra para completarse adicionalmente conduce a un rendimiento global menor del producto deseado. Para esta reacción, la terminación deseada de la reacción se alcanzó en 2,75 h. Después se cargó lentamente MTBE (5,1 l) al reactor, haciendo que el producto precipitara y la suspensión se agitó durante 30 minutos más. La mezcla se filtró, se lavó dos veces con 1:1 de DCM/MTBE (2 x 1l) y se secó en una estufa de vacío durante una noche a 50°C para proporcionar 500,3 g (74%) de 5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído en forma de un sólido blanquecino. ^{1}H RMN (300 MHz, d_6-

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DMSO): 2,64 (s, 3), 2,78 (d, 3, J = 0,8), 7,36 (d, 1, J = 0,9), 10,13 (s, 1).

Ejemplo (C4): Preparación de 2-(4-bromo-2-fluorofenil)-2-metilpropanonitrilo

Etapa A: 2-(4-Bromo-2-fluorofenil)-2-metilpropanonitrilo

Un matraz de 5 l, de 3 bocas se cargó secuencialmente con cianuro sódico (342,19 g, 6,982 moles), Bu_4NBr (49,29 g, 0,1529 mol), agua (800 ml) y CH_2Cl_2 (800 ml). Después de la disolución, la solución se enfrió a 10°C. En un recipiente separado, se añadió CH_2Cl_2 (320 ml) a 4-bromo-2-fluorobromuro de bencilo (1628,87 g, 6,080 mol) y la mezcla se agitó y se calentó a temperatura ambiente hasta su disolución. La solución de bromuro de 4-bromo-2-fluorobencilo/CH_2Cl_2 se cargó a un embudo de adición y se añadió lentamente a la solución de cianuro agitada con el fin de controlar la exotermia de la reacción, manteniendo la temperatura interna entre 25-30 °C. Una vez completada la adición, se retiró una alícuota y se analizó por HPLC, mostrando una proporción 2,2:1 de producto a material de partida. La temperatura del baño se ajustó a ta y la reacción se agitó 19 h más. El análisis por HPLC no mostró material de partida detectable. La solución se añadió a un embudo de separación y se retiró la capa acuosa inferior. A la fase orgánica se le añadió una solución acuosa de $NaHCO_3$ al 1% (8 g de $NaHCO_3$ en 800 ml de agua) y éter isopropílico (IPE, 1600 ml) y las fases se mezclaron bien. La fase acuosa es ahora la capa superior. Las capas se separaron y la fase orgánica inferior se volvió a añadir al embudo de separación y se extrajo de nuevo con una solución ac. de $NaHCO_3$ al 1% (800 ml). Las fases se separaron y la capa orgánica se añadió a un matraz de 5 l, de 3 bocas equipado para destilación. La solución se destiló a presión atmosférica hasta un volumen interno de ~1,6 l. A la solución se le añadió IPE (800 ml) y se continuó la destilación hasta que el volumen fue de ~1,5 l. Se añadió más IPE (500 ml) y la solución se destiló hasta un volumen interno de 1,6 l. Después de completarse el desplazamiento del disolvente, la solución se dejó enfriar a 29 °C durante 2 horas y después se sembró con 2-(4-bromo-2-fluorofenil)-2-metilpropanonitrilo cristalino, provocando una exotermia a 36 °C. La solución se dejó enfriar con agitación vigorosa durante una noche. Después, la suspensión se enfrió en un baño de hielo/agua hasta una temperatura interna <10 °C durante 1,5 h. La suspensión fría se filtró y los sólidos se aclararon con éter isopropílico frío (2 x 250 ml, <5 °C). Los sólidos se secaron al vacío (sin calentamiento, el sólido funde a <40°C) para proporcionar 1104,80 g (65%) de producto en forma de un sólido blanquecino cristalino con una pureza de 99,8% por HPLC. ^1H RMN de (300 MHz, $CDCl_3$): 3,64 (s, 2), 7,27-

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7,42 (m, 3).

Etapa B:

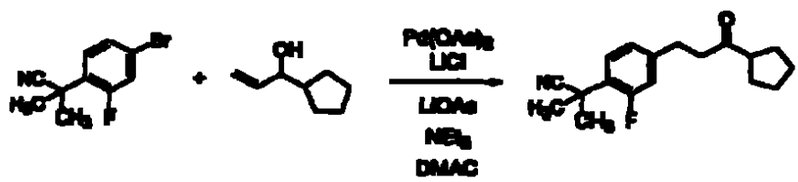


Un matraz de 2 litros y de 3 bocas se cargó con (4-bromo-2-fuorofenil)acetonitrilo (100,91 g, 0,4715 mol), MeOTs (156 ml g, 1,034 mol), DMF (400 ml) y THF (400 ml). El espacio de cabeza se purgó con nitrógeno y la solución se enfrió a -10°C. El NaOtBu (96,58 g, 1,005 mol) se dividió en 4 porciones iguales que se añadieron por separado a la reacción para controlar la exotermia. Cinco minutos después de la carga cuarta y final, se retiró una alícuota y se analizó por HPLC, verificando que la reacción se había completado. Se retiró el baño frío y se permitió que la reacción se agitara sin enfriamiento (temperatura interna = 4°C). El matraz se cargó después con DABCO (13,02 g, 0,116 mol) para consumir el MeOTs restante. Después de 30 min se retiró una alícuota y se analizó por HPLC, mostrando que no había MeOTs detectable. El matraz se cargó con H_2O (400 ml) y hexanos (400 ml) y la mezcla se añadió a un embudo de separación. Las fases se mezclaron bien y después se separaron. La fase acuosa se volvió a cargar en el embudo de separación y se volvió a extraer con hexanos (200 ml). Las fases orgánicas de las primeras dos extracciones se combinaron y se transfirieron a un embudo de separación y se lavaron dos veces con H_2O (200 ml). Las fases se separaron y la capa orgánica se añadió a un matraz de 2 l, de 3 bocas equipado para destilación. La solución se destiló al vacío (400 torr con una temperatura interna de aproximadamente 50°C) hasta que no ocurrió una destilación significativa del disolvente. Se retiró una alícuota de la solución y se analizó por ^{1}H RMN para registrar la cantidad de disolventes presente. La solución de producto se mantuvo durante una noche y se usó sin procesado adicional en la siguiente etapa. Para control por HPLC, se extrajeron alícuotas y se disolvieron en CH_3CN/H_2O (70:30). Condiciones de HPLC: columna Kromasil C4, Sum, 4,6x150mm, cámara de la columna a 40 °C, caudal = 1,0 ml/min, CH_3CN al 70%/acuoso al 30% (1,0 ml de $HClO_4$ al 70% en 1 l de H_2O) isocrático. Los porcentajes se presentan a 215 nm. Tiempos de retención: material de partida = 2,7 min, producto = 3,3 min, MeOTs = 2,5 minutos, producto mono-alquilado = 3,1 min. ^{1}H RMN (300 MHz, $CDCl_3$): 6,90-7,00 (m, 2), 7,33-7,39 (m, 1)

Ejemplo (C5): Preparación de 2-[4-(3-ciclopentil-3-oxopropil)-2-fluorofenil]-2-

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metilpropanonitrilo

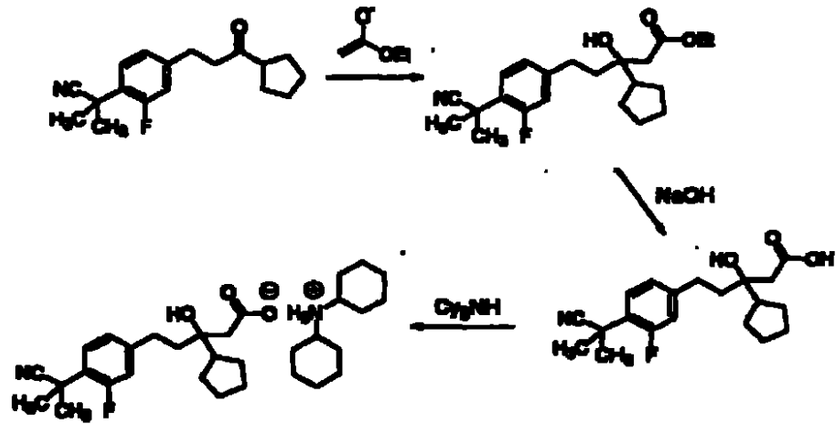


Un matraz de 2 l, de 3 bocas purgado con nitrógeno que contenía 2-(4bromo-2-fluorofenil)-2-metilpropanonitrilo (114,14 g, 0,4715 mol) se cargó secuencialmente (mientras se agitaba) con LiCl (39,62 g, 0,9347 mol), LiOAc (15,41, 0,2334 mol), DMAc (283 ml) y H_2O (28,3 ml). La solución se purgó después (subsuperficialmente) con N_2 durante 1 h. El matraz se cargó después con 1-ciclopentil-prop-2-en-1-ol (73,70 g, 0,5808 mol), Et3N (6,5 ml, 0,0466 mol, 10% del total a añadir) y $Pd(OAc)_2$ (5,2487 g, 0,0234 mol) seguido de una purga cuidadosa del espacio de cabeza. La reacción se calentó hasta 75°C. Una vez que la temperatura interna alcanzó los 60°C la reacción puede crear una exotermia. Tarda un total de 20 minutos en calentar la reacción a 75 °C. Quince minutos después de que la temperatura interna haya alcanzado los 60 °C, se retiró una alícuota y se analizó por HPLC, mostrando una relación 3:1 de material de partida a producto. En este punto se añadió una segunda adición de NEt3 (13,0 ml, 0,0933 mol, 20% del total a añadir) a la reacción. Cada adición de TEA provoca exotermias adicional es. Veinte minutos después de la segunda adición de NEt_3, se retiró una alícuota y se analizó por HPLC, mostrando una relación 2:1 de material de partida a producto. Diez minutos más tarde, se añadió la tercer porción de NEt_3 (46,0 ml, 0,3300 mol, 70% del total a añadir) a la reacción. Treinta y cinco minutos después de la adición final de NEt_3, se retiró una alícuota y se analizó por HPLC, mostrando una relación >70:1 de producto a material de partida. La reacción se calentó durante 30 min más, después se enfrió a <30°C durante 15 min. El matraz se cargó con H_2O (500 ml), MTBE (500 ml), DARCO (28,5 g) y celite (28,5 g). La solución se agitó bien durante 2 horas y después se filtró sobre una torta de celite (28,5 g cargados en un embudo buchner de 10,16 cm). esta filtración de la bicapa a través de celite fue lenta y el vacío provocó que una porción significativa del disolvente orgánico se evaporara. La torta se lavó con MTBE (250 ml seguido de 125 ml). El filtrado se añadió a un embudo de separación con una porción adicional de MTBE (200 ml), las fases se mezclaron bien y la capa acuosa se retiró. La fase orgánica se extrajo con H_2O (200 ml) y las fases se mezclaron bien. La capa acuosa inferior se retiró. La capa orgánica se extrajo con una solución de NaCl al 5%/H_2O (200 ml). Las fases se separaron y la capa orgánica se añadió a un matraz de 1 l, de 3 bocas. La solución se concentró por destilación atmos-

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férica hasta que el volumen interno fue de -2 volúmenes. Después de enfriar por debajo del reflujo, se retiró una alícuota y se analizó por titulación con K-F, mostrando un 0,35% de H_2O. Se añadió una porción adicional de MTBE (150 ml) y la destilación continuó hasta que el volumen interno fue de nuevo de -2 volúmenes. Después de enfriar por debajo del reflujo, se retiró una alícuota y se analizó por titulación con K-F, mostrando un 0,14% de H_2O. La solución se enfrió en atmósfera de nitrógeno y se mantuvo durante una noche a ta. La solución se usó directamente en la siguiente reacción sin procesado adicional. ^1H RMN (300 MHz, $CDCl_3$): 1,52-1,72 (m, 9), 1,77 (s, 6), 2,73-2,92 (*m*, 4), 6,90-7,00 (*m*, 1), 7,33-7,39 (*m*, 1)

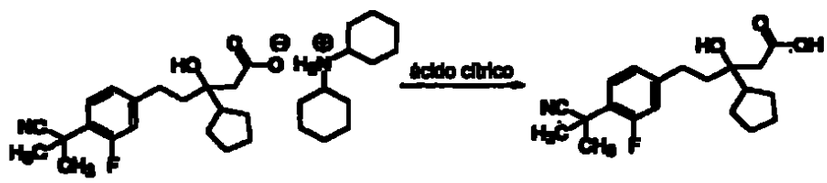
Ejemplo (C6): Preparación de sal de ciclohexilamina del ácido 5-[4-(1-ciano-1-metiletil)-3-fluorofenil]-3-ciclopentil-3-hidroxipentanoico



Se cargó un matraz de 3 l, de 3 bocas con LIHMDS (1,0 M en THF, 750 ml, 0,75 mol) y se purgó con nitrógeno. La matraz se enfrió a -34°C. Después se cargó un embudo de adición con EtOAc (74 ml, 0,7576 mol) y este reactivo se añadió lentamente al recipiente de reacción. Después de completar la adición de EtOAc se cargó otro embudo de adición con una solución de 2-[4-(3-ciclopentil-3-oxopropil)-2-fluorofenil]-2-metilpropanonitrilo (solución de MTBE bruto de la reacción anterior, teórico. 135,49 g, 0,4715 mol) y se aclaró sobre THF (*anhidro*, 20 ml). La solución de cetona se añadió al matraz de reacción. Cinco minutos después de completar la adición se retiró una alícuota de reacción y se analizó por HPLC, mostrando un 1% de 2-[4-(3-ciclopentil-3-oxopropil)-2-fluorofenil]-2-metilpropanonitrilo. Diez minutos después de completar la adición de cetona, el baño se cambió a 0°C. Una vez que la temperatura interna se había calentado a -10°C, se añadió lentamente NaOH 1 M (660 ml). Después de completar la adición de la solución de NaOH, la reacción se calentó a 50°C. Después de 21

horas se retiró una alícuota de la capa superior y se analizó por HPLC, mostrando que no había 5-[4-(1-ciano-1-metiletil)-3-fluorofenil-3-ciclopentil-3-hidroxipentanoato de etilo detectable. La solución de reacción se enfrió por debajo de 30ºC y se añadió a un embudo de separación con MTBE (1265 ml). Las fases se mezclaron bien y se separaron. Se analizó una alícuota de la fase acuosa por HPLC, verificando que no había producto significativo y esta capa se desechó. Se añadió agua (1265 ml) y las fases se mezclaron bien y se separaron. Se analizó una alícuota de la fase orgánica por HPLC, verificando que había poco producto en esta capa y la fase orgánica se desechó. La fase acuosa se añadió al matraz. Se añadió HCl acuoso concentrado (~49 ml) a la fase acuosa hasta un pH = 2. La mezcla se volvió a añadir al embudo de separación con IPE (1265 ml) y se mezcló bien. Una alícuota de la fase acuosa verificó que no había producto significativo y esta capa se desechó. La capa orgánica se secó ($MgSO_4$, 25 g), se filtró y la torta se aclaró con IPE (200 ml). La solución se analizó por valoración con K-F, mostrando un contenido de agua del 0,93%. esta solución se cargó a un matraz de 3 l, de 3 bocas. Agitando bien, se añadió diciclohexilamina (188 ml, 0,9446 mol). La adición de amina provocó una exotermia a 28 ºC. Después de 10 min, se observaron sólidos significativos. La solución se agitó a ta durante 2,5 h. La solución se enfrió en un baño a 0ºC hasta que la temperatura interna permaneció por debajo de 5ºC durante 2 h. La suspensión se filtra y los sólidos se enjuagaron con IPE frío (5ºC) (250 ml). Los sólidos se secaron para proporcionar 189,68 g de sal de hidroxilamina del ácido 5-[4-(1-ciano-1-metiletil)-3-fluorophenyq-3-ciclopentil-3-hidroxipentanoico en forma de un polvo blanco. Los sólidos tenían una pureza del 98,4% por HPLC y estaban limpios según ^1H RMN.

Ejemplo (C7): Preparación de ácido 5-[4-(1-ciano-1-metiletil)-3-fluorofenil]-3-ciclopentil-3-hidroxipentanoico

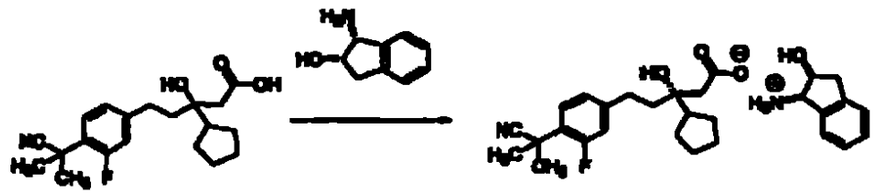


Se cargó un matraz de 3 l, de 3 bocas con sal diciclohexilamina del ácido 5-[4-(1-ciano-1-metiletil)-3-fluorofenil]-3-ciclopentil-3-hidroxipentanoico (166,0 g, 0,314 moles) y NITRE (1,7 l). La suspensión se agitó a 22ºC y se añadió ácido cítrico acuoso al 10%. La mezcla se agitó durante 45 minutos. La mezcla se añadió a un embudo de separación y se retiró la fase acuosa inferior. La solución orgánica se lavó con H_2O (50

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ml) y se puso en un matraz de 2 l, de 3 bocas. La solución se destiló a presión atmosférica a ~2,5 volúmenes, empezando la temperatura del destilado a aproximadamente 52°C y estabilizándose a ~56°C. La solución de ácido 5-[4-(1-ciano-1-metiletil)-3-fluorofenil]-3-ciclopentil-3-hidroxipentanoico (teórico 0,314 mol) se usó directamente en la siguiente etapa.

Ejemplo (C8): Preparación de sal de (1R,2S)-(+)-cis-1-amino-2-indanol del ácido (3R)-5-[4-(1-ciano-1-metiletil)-3-fluorofenil]-3-ciclopentil-3-hidroxipentanoico



Un matraz de 2 l, de 3 bocas se cargó con (1R,2S)-(+)-cis-1-amino-2-indanol (23,40 g, 0,157 moles) y THF (580 ml). La mezcla se agitó y se calentó a 50°C, observándose en este punto una solución homogénea. A la solución calentada se le añadió una solución de ácido 5-[4-(1-ciano-1-metiletil)-3-fluorofenil]-3-ciclopentil-3-hidroxipentanoico (109,10 g en MTBE, 0,314 moles, 425 ml de volumen total) a una velocidad tal que la temperatura interna se mantuvo por encima de 47°C. Una vez completada la adición, se añadió MTBE (350 ml) a una velocidad tal que la temperatura interna se mantuvo por encima de 47°C. La mezcla agitada se sembró inmediatamente después de completar la adición de la segunda porción de MTBE (la cristalización progresó rápidamente después de sembrar la mezcla). Después de la siembra, se interrumpió el calentamiento y se dejó que la mezcla se enfriara gradualmente a ta. La mezcla se agitó durante 17 horas a 21°C. La mezcla se filtró y los sólidos se aclararon con 1:1 de MTBE/THF (190 ml). Los sólidos se secaron en un horno de vacío (~25 mmHg,50°C) durante 24 h para proporcionar 66,10 g (42 %) de sal (1R,2S)-(+)-cis-1-amino-2-indanol del ácido (3R)-5-[4-(1-ciano-1-metiletil)-3-fluorofenil]-3-ciclopentil-3-hidroxipentanoico en forma de un sólido cristalino blanquecino (el rendimiento representa una recuperación del 85% del rendimiento máximo del 50% para la sal diastereoméricamente pura). El análisis de HPLC quiral del ácido mostró que el producto tenía un 98% de ee.

Recristalización de la sal de (1 R,2S)-(+)-cis-1-amino-2-indanol del ácido (3R)-5-[4-(1-ciano-1-metiletil)-3-fluorofenil]-3-ciclopentil-3-hidroxipentanoico: Un matraz de 3 litros y de tres bocas se cargó con sal de (1R,2S)-(+)-cis-1-amino-2-indanol del ácido (3R)-5-[4-(1-ciano-1-metiletil)-3-fuorofenil]-3-ciclopentil-3-hidroxipentanoico (65,40 g,

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0,132 moles) e IPA (1,7 L). La suspensión se agitó y se calentó a 80°C hasta que se disolvieron todos los sólidos. A 80 °C, la solución se sembró con sal de (1R,2S)-(+)-cis-1-amino-2-indanol del ácido (3R)-5-[4-(1-ciano-1-metiletil)-3-fluorofenil]-3-ciclopentil-3-hidroxipentanoico y se interrumpió el calentamiento. A 75°C, la solución se sembró de nuevo y en este punto empezó a ocurrir una cristalización secuencial. La mezcla agitada se dejó enfriar a ta y se granuló durante 22 h. La mezcla se filtró después y los sólidos se enjuagaron con IPA (60 ml). Los sólidos se secaron en una estufa de vacío (-25 mmHg,50°C) durante 48 h para proporcionar 60,13 g (92%) del producto en forma de un sólido blanco cristalino. El análisis por HPLC quiral del ácido mostró un producto con >99% *ee*.

Para determinar el e.e., el sólido se disolvió en CH_3CN/H_2O (70/30). Condiciones de HPLC: Columna Chiralcel OJ-RH,5 µm, 4,6 x 150 mm, cámara de la columna a 30 °C, caudal = 0,8 ml/min, H_2O al 55% (TFA al 0,1%)/CH_3CN al 45% (TFA al 0,1%). Los porcentajes se presentan a 205 nm. Tiempos de retención: (1R,2S)-(+)-cis-1-amino-2-indanol = 2,2 a 2,4 min; ácido (3R)-5-[4-(1-ciano-1-metiletil)-3-fluorofenil]-3-ciclopentil-3-hidroxipentanoico = 6,4 min; enantiómero indeseado = 7,1 min. La HPLC quiral del filtrado indicó una mezcla 5:1 del enantiómero indeseado con respecto al enantiómero deseado. ^{1}H RMN (300 MHz, d_6-DMSO): 1,36-1,62 (m, 8), 1,62-1,74 (m, 2), 1,70 (s, 6), 1,90-2,04 (m, 1), 2,17 (1, d, J = 15,3), 2,23 (1, d, J = 15,3), 2,58-2,68 (m, 2), 2,89 (dd, 1, J = 3,3, 16,2), 3,07 (dd, 1, J = 5,8, 16,2), 4,39 (d, 1, J = 5,5), 4,52 (dt, 1, J = 3,3,5,6), 7,03-7,47 (m, 7).

Ejemplo (C9): Preparación de ácido (3R)-5-[4-(1-ciano-1-metiletil)-3 fluorofenil]-3-ciclopentil-3-hidroxipentanoico



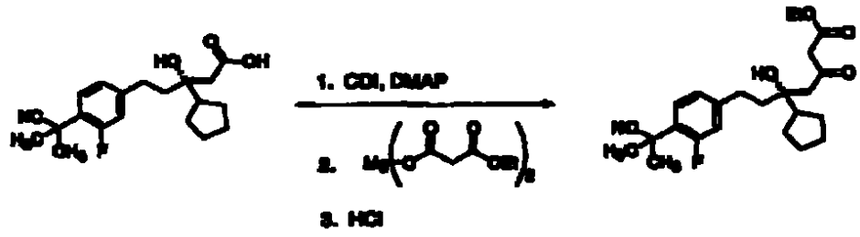
Un matraz de 2 litros y 3 bocas se cargó con sal de (1 R,2S)-(+)-cis-1 -amino-2-indanol del ácido (3R)-5-[4-(1-ciano-1-metiletil)-3-fluorofenil]-3-ciclopentil-3-hidroxipentanoico (59,009, 0,119 moles) y MTBE. La mezcla se agitó a ta y se añadió una solución acuosa de ácido cítrico al 10%. Después de agitar durante tres horas (si todavía hay sólidos presentes, puede necesitarse un tiempo de mezcla adicional), la mezcla se añadió a un embudo de separación enjuagando el reactor con MTBE (50 ml) y se retiró la capa acuosa inferior. La fase orgánica se lavó con H_2O (20 ml). La fase

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orgánica que contenía ácido (3R)-5-[4-(1-ciano-1-metiletil)-3-fluorofenil]-3-ciclopentil-3-hidroxipentanoico era >99% pura por HPLC. La solución orgánica húmeda se puso en un matraz de 1 litro y 3 bocas y la solución se destiló a presión atmosférica para retirar el H_2O (volumen de partida = 785 ml; volumen después de la destilación = 170 ml). La solución se filtró y se cargó a embudo de adición de 250 ml. esta solución se usó directamente en la siguiente etapa.

Análisis HPLC de las fases acuosa y orgánica: Las alícuotas se retiraron y se disolvieron en CH_3CN/H_2O (70/30). Condiciones de HPLC: Columna Kromasil C4,5 µm, 4,6 x 150 mm, cámara de la columna a 40 °C, caudal = 1,0 ml/min, CH_3CN al 70%/ acuoso al 30% (1,0 ml de $HClO_4$ al 70% en 1 l de H_2O) isocrático. Los porcentajes se presentan a 215 nm. Tiempo de retención: ácido (3R)-5-[4-(1-ciano-1-metiletil)-3-fluorofenil]-3-ciclopentil-3-hidroxipentanoico = 2,7 min.

Ejemplo (C10): Preparación de (5R)-7-[4 (1-ciano-1-metiletil)-3-fluorofenil]-5-ciclopentil-5-hidroxi-3-oxoheptanoato de etilo



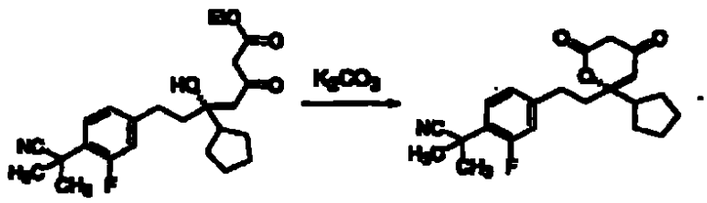
Un matraz de 1 l, de 3 bocas se cargó con CDI (29,00 g, 0,179 moles), DMAP (733 mg, 0,006 moles) y MTBE (70 ml) (notas 1, 2). Se añadió una solución de MTBE de ácido (3R)-5-4-(1-ciano-1-metiletil)-3-fluorofenil]-3-ciclopentil-3-hidroxipentanoico (41,28 g, 0,119 moles, 170 ml) a la mezcla agitada durante un periodo de 30 minutos. El embudo de adición se aclaró con THF (5 ml) y el aclarado se añadió a la mezcla de reacción. La mezcla se agitó durante 30 min y se retiró una alícuota y se analizó por HPLC. Una vez completada la formación de acil-imidazol, la solución se añadió a un embudo de adición de 500 ml. Se cargó un matraz de 1 l, de 3 bocas diferente con malonato de etil magnesio (51,30 , 0,179 moles) y THF (100 ml) (los sólidos no se disolvieron en THF, incluso después de calentar a 40°C). La mezcla agitada se calentó a 40°C y la solución de acil-imidazol se añadió lentamente a la mezcla. Se continuó agitando a 40°C y se retiraron alícuotas periódicamente y se analizaron por HPLC para evaluar la finalización. Una vez completada la reacción, se interrumpió el calentamiento y la solución se dejó enfriara a temperatura ambiente. La solución se diluyó con IPE (200 ml) y

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HCl 1 N (360 ml), la mezcla se agitó durante 15 minutos y las fases se separaron. La fase orgánica se extrajo con H_2O (10 ml), las fases se separaron y la capa orgánica se añadió a un matraz de 1 l, de 3 bocas. La solución se destiló hasta un mínimo de ~3,3 volúmenes para retirar el H_2O (la temperatura del destilado fue de 48 °C durante la destilación azeotrópica y la destilación terminó después de que la temperatura del destilado se mantuviera a ~50 °C). La solución se usó directamente en la siguiente etapa.

Para control por HPLC, se extrajeron alícuotas y se disolvieron en CH_3CN/H_2O (70/30). Condiciones de HPLC: Columna Kromasil C4,5 µm, 4,6 x 150 mm, cámara de la columna a 40 °C, caudal = 1,0 ml/min, CH_3CN al 70%/acuoso al 30% (1,0 ml de $HClO_4$ al 70% en 1 l de H_2O) isocrático. Los porcentajes se presentan a 215 nm. Tiempo de retención: Imidazol = 1,4 min, acil-imidazol = 2,2 min, subproducto de anhídrido = 2,4 min, (5R)-7-[4-(1-ciano-1-metiletil)-3-fluorofenil]-5-ciclopentil-5-hidroxi-3- oxoheptanoato de etilo = 2,7 min. ^1H RMN (300 MHz, $CDCl_3$): 1,29 (t, 3, J = 7,2), 1,40-1,55 (m, 3), 1,57-1,72 (m, 6), 1,86 (m, 6), 2,12 (m, 1), 2,65 (m, 2), 2,82 (d, 1, J = 5,1), 3,66 (m, 2), 3,76 (m, 3), 4,22 (q, 2, J = 7,2), 6,97 (m, 2), 7,38 (t ap., 1, J = 8,1).

Ejemplo (C11): Preparación de 2-(4{2-[(2R)-2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il]etil}2-fluorofenil)-2-metilpropanonitrilo



Se cargó una solución de (5R)-7-[4-(1-ciano-1-metiletil)-3-fluorofenil]-5-ciclopentil-5-hidroxi-3-oxoheptanoato de etilo (49,61 g, 0,1188 mol, 135 ml de volumen total) en un matraz de 1 l, de 3 bocas con MeOH (120 ml) y K_2CO_3 (25,00 g, 0,1809 mol) y la mezcla agitada se calentó a 50°C durante 4 horas. Se retiró una alícuota y se analizó por HPLC y mostró que la reacción se había completado en más del 99%. La solución se enfrió a ta y se cargó con IPE (50 ml) y H_2O (200 ml). La mezcla se agitó durante 5 minutos y se puso en un embudo de separación de 2 l para separar las fases. El recipiente de reacción se aclaró con H_2O (10 ml) y el enjuague se añadió al embudo de separación. Las fases se separaron y la fase acuosa que contenía el producto se extrajo con IPE (20 ml). Las capas se separaron y la fase acuosa se volvió a añadir al embudo. A la fase acuosa se le añadió 2-Me THF (300 ml), MTBE (100 ml) y HCl 1 M (~360 ml) hasta que el pH de la fase acuosa fue de 4,75. Las fases se mezclaron bien y

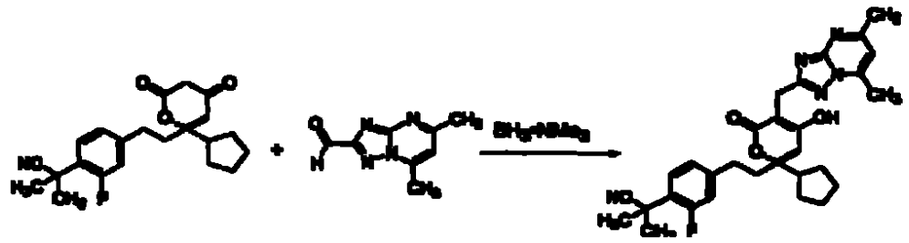
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la fase acuosa se retiró. La fase orgánica se lavó con H_2O (20 ml) y se puso en un matraz de 500 l, de 3 bocas. La solución se concentró por destilación atmosférica a ~3,3 vol. (la temperatura del destilado durante la formación del azeótropo empezó a 38°C, después aumentó a 48°C y finalmente se estabilizó a 57°C). La solución se enfrió a 25°C y se analizó una alícuota por valoración de Karl-Fischer. La solución después se calentó de nuevo a 55 °C y se añadió heptano (50 ml) a una velocidad tal como para mantener la temperatura interna por debajo de 53 °C (la adición de heptano cuando la temperatura interna estaba por debajo de 50 °C hizo que se transformara en una solución aceitosa). La solución se sembró después con 2-(4-[2-[(2R)-2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il]etil]-2-fluorofenil)-2-metilpropanonitrilo sólido, seguido de la adición de heptano (250 ml). Se permitió que la mezcla agitada se enfriara gradualmente a ta. Después de agitar durante 15 min a ta, la mezcla se filtró y los sólidos se enjuagaron con IPE/heptano 1:1 (75 ml). Los sólidos se secaron para proporcionar 30,92 g (70%) de 2-(4-2-[(2R)-2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il]etil]-2-fluorofenil)-2-metilpropanonitrilo en forma de cristales granulares. Los sólidos se secaron al vacío en un horno de vacío (~25 mmHg,50°C) durante 20 h y se determinó que eran >98% puros mediante análisis por HPLC.

Condiciones de HPLC: Las alícuotas e retiraron y se disolvieron en CH_3CN/H_2O (80/20). Condiciones de HPLC: Columna Kromasil C4,5 µm, 4,6 x 150 mm, cámara de la columna a 40 °C, caudal = 1,0 ml/min, CH_3CN al 80%/acuoso al 20% (1,0 ml de $HClO_4$ al 70% en 1 l de H_2O) isocrático. Los porcentajes se presentan a 215 nm. Tiempo de retención: 2-(4-[2-[(2R)-2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il]etil]2-fluorofenil)-2-metilpropanonitrilo = 2,2 min, (5R)-7-[4-(1-ciano-1-metiletil)-3-fluorofenil]-5-ciclopentil-5-hidroxi-3-oxoheptanoato de etilo = 2,7 min, sub-producto 1 = 2,8 min, sub-producto 2 = 2,9 min, sub-producto 3 = 3,1 min. ^1H RMN (300 MHz, $CDCl_3$): 1,46-1,73 (m, 7), 1,77 (s, 7), 1,91(m, 2), 2,27 (m, 1), 2,68 (t, 2, J = 7,8), 2,77 (s, 2), 3,43 (d, 2, J = 1,4), 6,92 (m, 2), 7,39 (t ap., 1, J = 8,2).

Ejemplo (C12): Preparación de 2-[4-(2-{ (2R)-2-ciclopentil-6-[(5,7-dimetil[1,2,4]triazolo(1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo

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Un matraz de 1 l, de 3 bocas se cargó secuencialmente con 2-(4-[2-[(2R)-2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il]etil}-2-fluorofenil)-2-metilpropanonitrilo (30,01 g, 0,0808 moles), e IPA (150 ml). Después de purgar con N_2, el matraz se cargó con BH3•NMe3 (8,27 g, 0,113 moles) y 5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidina-2-carbaldehído (21,37 g, 0,121 moles). Después de 15 min se retiró una alícuota y se analizó por HPLC (típicamente, el material de partida está en el intervalo de 5-8% antes de inactivar). El matraz se cargó con acetato de isopropilo (IPAc, 150 ml) y HCl 1 M (150 ml). Después de 30 min se retiró una alícuota y se analizó por HPLC para verificar la descomplejación del boro. La reacción se transfirió a un embudo de separación y la fase acuosa se retiró. La fase orgánica se extrajo con H_20 (150 ml) y la capa acuosa se retiró. La capa orgánica se añadió a un matraz de 500 ml, de 3 bocas equipado para destilación. La solución se destiló hasta un nivel mínimo de 5 vols., se añadió IPAc (100 ml) y se continuó la destilación. este proceso se repitió hasta que se retiró el IPA de la solución y la destilación se continuó para conseguir 5 vol. (la destilación se juzgó completa cuando el cabezal de destilación mantuvo una temperatura estacionaria de aproximadamente 86-89°C). La solución se enfrió lentamente a temperatura ambiente y se agitó durante una noche. La mezcla se filtró y los sólidos se lavaron con IPAc (2 x 25 ml). Los sólidos se transfirieron a un matraz de 1 litro y de 3 bocas con IPAc (150 ml) e IPA (150 ml) y se calentaron a 50 °C. La solución se enfrió a una temperatura interna de 30 °C y se filtró a través de un filtro de membrana de 0,45 µm. El matraz se aclaró con una mezcla de IPAc/IPA (1:1, 100 ml). El filtrado se puso en un matraz de 500 ml, de 3 bocas equipado para destilación. La solución se destiló a un nivel mínimo de 5 vol. Después se cargó IPAc (100 ml) y se continuó la destilación. El proceso se repitió hasta que se retiró el IPA de la solución y la destilación se continuó para conseguir 5 vol. (la destilación se juzgó completa cuando el cabezal de destilación mantuvo una temperatura estacionaria de aproximadamente 86-89°C). La solución se enfrió lentamente a ta y se agitó durante una noche. La mezcla se filtró y los sólidos se lavaron con IPAc (2 x 25 ml) y se secaron en un horno de vacío (25 mmHg,50°C) durante una noche. Los sólidos secos se cargaron en un matraz con H_2O (500 ml - calidad HPLC), se calentaron a 75 °C y se agitaron vigorosamente durante 16 h. La suspensión se enfrió, se filtró sobre

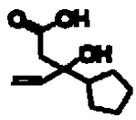
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polycloth y los sólidos se lavaron con H_2O (2 x 100 ml) y se secaron en una estufa de vacío (25 mm Hg,50ºC) durante una noche para proporcionar 23,58 g (55%) de 2-[4-(2-((2R)-2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo en forma de un sólido cristalino blanco.

Para control por HPLC, se extrajeron alícuotas y se disolvieron en CH_3CN/H_2O (70:30). Condiciones de HPLC: Columna Kromasil C4,5µm, 4,6x150mm, cámara de la columna a 40ºC, caudal= 1,0 ml/min, CH_3CN al 70%/acuoso al 30% (1,0 ml de $HClO_4$ al 70% en 1 l de H_2O) isocrático. Los porcentajes se presentan a 215 nm. Tiempos de retención: 2-(4-[2-[(2R)-2-ciclopentil-4,6-dioxotetrahidro-2H-piran-2-il]etil]-2-fluorofenil)-2-metilpropanonitrilo = 2,67 min,5,7-dimetil[1,2,4]triazolo(1,5-a]pirimidina-2-carbaldehído = 1,5 min, 2-[4-(2-[(2R)-2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo(1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo = 2,3 min, complejo de boro/pdt. = 2,6 min

El producto no contenía enantiómero detectable mediante análisis por HPLC quiral. Para determinar el e.e., el sólido se disolvió en CH_3CN/H_2O (70/30). Condiciones de HPLC: Columna Chiralcel OJ-RH,5 µm, 4,6 x 150 mm, cámara de la columna a 30 ºC, caudal = 0,8 ml/min, H_2O al 55% (TFA al 0,1%)/CH_3CN al 45% (TFA al 0,1%). Los porcentajes se presentan a 205 nm. Tiempos de retención: enantiómero indeseado = 6,3 min, 2-[4-(2-[(2R)-2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo(1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-2-fluorofenil]-2-metilpropanonitrilo = 7,3 min. ^1H RMN (300 MHz, $CDCl_3$): 1,32-1,83 (m, 8), 1,80 (s, 6), 1,99-2,08 (m, 2), 2,33-2,48 (m, 1), 2,58 (d, 1, J = 17,7), 2,63-2,76 (m, 2), 2,71 (s, 3), 2,82 (d, 1, J = 17,7), 2,83 (s, 3), 4,14 (s a, 2), 6,87-6,98 (m, 3), 7,37 (t ap., 1, J = 8,2).

Ejemplo C(13): Ácido 3-ciclopentil-3-hidroxipent-4-enoico

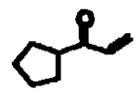


Se disolvió 3-ciclopentil-3-hidroxipent-4-enoato de etilo (22,12 g, 104,34 mmol), de la etapa 2 mostrada a continuación, en MeOH (100 ml) y se añadió una solución de NaOH (8,35 g) en H_2O (100 ml). La reacción se agitó durante una noche a temperatura ambiente. La mezcla de reacción se repartió entre H_2O e IPE. La capa acuosa se acidificó con HCl 4 N y se extrajo con EtOAc. Las capas orgánicas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron para dar un sólido blanquecino que se

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recristalizó en hexanos calientes. (18g, rendimiento de 94%) ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,26-1,69 (m, 8H), 1,99-2,08 (m, 1H), 2,60 (d, J = 15,6, 1H), 2,68 (d, J = 15,6, 1H),5,17-5,33 (m, 2H),5,82-5,92 (m, 1H). ESIMS (MH-): 183.

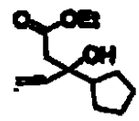
Etapa 1: 1-Ciclopentil-propenona



Se disolvió ácido ciclopentano carboxílico (15 ml, 138,41 mmol) en CH_2Cl_2 (185 ml) y DMF (0,25 ml). La reacción se enfrió a 0 °C y se añadió lentamente cloruro de oxalilo (13,9 ml, 159,19 mmol). Después de agitar durante 1 hora a temperatura ambiente, se enfrió de nuevo a 0 °C y se añadió lentamente mediante un embudo de adición una solución de $AlCl_3$ (20,30 g, 152,28 mmol) y viniltrimetilsilano (21,38 ml, 138,44 mmol) en CH_2Cl_2 (190 ml). La mezcla de reacción se agitó durante 10 minutos y después se vertió en hielo. Se añadió HCl concentrado hasta que el precipitado de $Al(OH)_3$ se disolvió y las capas se separaron. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró hasta dar un aceite amarillo que se usó sin purificación adicional.

El aceite se disolvió en CH_3CN (100 ml), se trató con trietil amina (24 ml) y se agitó a 5 °C durante 1 hora. La mezcla de reacción se vertió en $KHSO_4$ al 5% (100 ml) y se extrajo con acetato de etilo (3x100 ml). Las capas orgánicas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron cuidadosamente (volátiles) para dar un aceite amarillo que se usó en bruto sin purificación adicional. (15,7g, rendimiento de 94%) ESIMS (MH-): 125.

Etapa 2: 13-Ciclopentil-3-hidroxipent-4-enoato de etilo

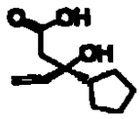


Una solución agitada magnéticamente de hexametildisilazina de litio 1 M en THF (253,23 ml) se enfrió a -78 °C. Se añadió cuidadosamente acetato de etilo (24,74 ml, 253,23 mmol) y la reacción se agitó durante 20 min a esta temperatura. Se disolvió 1-ciclopentil-propenona, de la etapa 1 anterior, en THF (40 ml) y se añadió al anión de litio mediante una cánula durante un periodo de 30 minutos. La reacción se agitó a -78 °C durante 1 hora. La mezcla de reacción se repartió entre HCl 1 N e IPE. Las capas de la mezcla de reacción resultante se separaron y la capa orgánica se lavó con sal-

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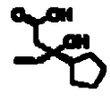
muera (1 x 10 ml), después se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El residuo bruto se purificó por cromatografía en columna ultrarrápida (EtOAc al 20% en hexanos) para dar el producto deseado en forma de un aceite amarillo (22,12 g, 81%). ^1H RMN (400MHz, $CDCl_3$): δ 1,25 (t, J = 7,2, 3H), 1,38-1,68 (m, 8H), 1,96-2,03 (m, 1H), 2,53 (d, J = 15,2, 1H), 2,60 (d, J = 15,2, 1H), 4,13 (q, J = 7,2, 2H),5,11-5,32 (m, 2H),5,80-5,90 (m, 1H). ESIMS (MH+): 213.

Ejemplo C(14): Ácido (3R)-3-ciclopentil-3-hidroxipent-4-enoico (ENANTIÓMERO 1)



A una solución de ácido 3-ciclopentil-3-hidroxipent-4-enoico (1 g,5,43 mmol) en EtOAc (27 ml) del ejemplo C(13) en agitación, se le añadió una solución de (S)-1,2,3,4-tetrahidnro-1-naftilamina* (0,399 g, 2,71 mmol) en EtOAc (13 mmol). Después de 10 minutos se formó un precipitado blanco. Este precipitado se recogió sobre papel y re-cristalizó en EtOAc caliente. El precipitado se repartió entre EtOAc (5 ml) y HCl 1 N (5 ml) y la capa orgánica se separó, se secó sobre Na_2SO_4 y se concentró al vacío hasta dar un aceite que solidificó tras reposo (0,43 g, 43%).
^1H RMN (300 MHz, $CDCl_3$): δ 1,26-1,69 (m, 8H), 1,99-2,08 (m, 1H), 2,60 (d, J = 15,6, 1H), 2,68 (d, J = 15,6, 1H),5,17-5,33 (m, 2H),5,82-5,92 (m, 1H). ESIMS (MH-): 183. 96% ee, Tiempo de retención 25,02 min (Chiralpack OD-RH, 150 x 4,6 mm,0,6 ml/min, 15% B y 85% tampón durante 30 min).
*Otras aminas adecuadas para la resolución son: (S)-(-)-1-(2-naftil)etilamina y (R)-(-)-1-(2-naftil)etilamina y (1R,2S)-(-)-norefedrina y (1S,2R)-(+)-norefedrina.

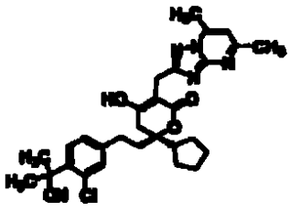
Ejemplo C(15): Ácido (3S)-3-ciclopentil-3-hidroxipent-4-enoico (ENANTIÓMERO 2)



El compuesto del título se prepara de una forma análoga al ejemplo C(14) (enantiómero 1) anterior sustituyendo (R)-1,2,3,4-tetrahidro-1-naftilamina en lugar de (S)-1,2,3,4-tetrahidro-1-naftilamina* de ese ejemplo. *Otras aminas adecuadas para la resolución son: (S)-(-)-1-(2-naftil)etilamina y (R)-(-)-1-(2-naftil)etilamina y (1R,2S)-(-)-norefedrina y (1S,2R)-(+)-norefedrina.

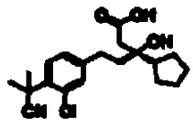
Ejemplo C(16): 2-[2-Cloro-4-(2{(2S)-2-ciclopentil-5-[(5,7-

dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)fenil]-2-metilpropanonitrilo.



El compuesto del título se preparó de una forma análoga al ejemplo A(1) sustituyendo 2-(2-cloro-4-[2-(2-ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]-fenil]-2-metil-propionitrilo, de la etapa 2 mostrada a continuación en lugar de 6-ciclopentil-6-[2-(5-etil-4-hidroxi-2-propoxi-fenil)-etil]-dihidro-piran-2,4-diona en ese ejemplo. ^{1}H RMN (400MHz, DMSO-d6): δ 1,39-1,64 (m, 8H), 1,67 (s, 6H), 2,01-2,05 (m, 2H), 2,36-2,46 (m, 7H), 2,51-2,57 (m, 2H), 2,69(d, J = 17 Hz, 2H), 3,61(d, J = 16 Hz, 1H), 3,72 (d, J = 16 Hz, 1H), 6,94 (s, 1H), 7,25 (s, 1H), 7,28 (s, 1H), 7,35 (d, J = 8 Hz, 1H), 10,75 (s, 1H). IR (puro): 2243, 2355 (CN), 1666, 1625, 1543, 1390, MS (ESI): 549 $(M+H)^+$. Rotación positiva. HPLC (Chiralpak AS-H, 140 Bar, 2,5 ml/min, MeOH al 35%) (tiempo de retención 12 min).

Etapa 1: Ácido 5-[3-cloro-4-(ciano-dimetil-metil)-fenil]-3-ciclopentil-3-hidroxi-pent-4-enoico

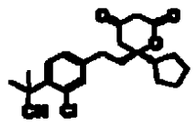


Una mezcla de 2-(4-bromo-2-cloro-fenil)-2-metil-propionitrilo (0,61g, 2,34 mmol), de la etapa 4 del ejemplo B(22), ácido (3R)-3-ciclopentil-3-hidroxipent-4-enoico (0,43 g, 2,34 mmol, ejemplo C(14), $Pd(OAc)_2$ (0,01 g,5% en moles) y NaOAc (0,24 g, 2,93 mmol) en DMAC (5 ml) se calentó a 90 °C durante una noche. La mezcla de reacción se enfrió a temperatura ambiente y se repartió entre HCl 1 N y EtOAc. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró hasta un aceite pardo oscuro. La cromatografía en columna ultrarrápida (EtOAc al 0%-40% en hexanos) dio un aceite pardo claro. El aceite se disolvió en EtOH (10 ml) y se trató con $Pd(OH)_2$ (0,23 g). La mezcla se agitó en un globo de hidrógeno durante 1 hora. La mezcla de reacción se filtró a través de una capa de celite lavando con EtOAc. El filtrado se concentró hasta dar un aceite naranja y se purificó por cromatografía en columna ultrarrápida para dar el producto en forma de un sólido amarillo (0,47g, 100%). ^{1}H RMN (300

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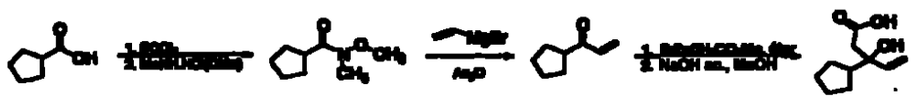
MHz, $CDCl_3$): δ 1,4-1,72 (m, 10 H), 1,85 (s, 6H), 2,11-2,18 (m, 1H), 2,58-2,73 (m, 4 H), 7,10 (d, J = 7,9 Hz, 1H) 7,26 (s, 1H), 7,36 (d, J = 7,9 Hz, 1H). ESIMS (MNa+): 364.

Etapa 2: 2-(2-Cloro-4-[2-(2-ciclopentil-4,6-dioxo-tetrahidro-piran-2-il)-etil]-fenil)-2 metil-propionitrilo.

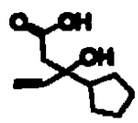


Se disolvió ácido 5-(3-cloro-4-(ciano-dimetil-metil)-fenil]-3-ciclopentil-3-hidroxi-pent-4-enoico, de la etapa 1 anterior, en terc-butil etilmalonato de metilo (3 ml). Se añadieron 4-DMAP (0,16 g, 0,13 mmol) y CDI (0,27 g, 1,68 mmol) y la mezcla de reacción se agitó en una atmósfera de argón durante 2 horas. En un matraz separado se puso bis-monoetil malonato de magnesio (0,74 g, 2,58 mmol), se suspendió en THF (3 ml) y la mezcla se calentó a 42 °C. La solución de acilimidazol se añadió mediante una cánula a la mezcla de malonato y la reacción se calentó a 42 °C durante 2 horas. El disolvente se retiró al vacío para dar un residuo que se repartió entre HCl 1 N y EtOAc. La capa orgánica se secó sobre $MgSO_4$ y se concentró hasta un aceite transparente (0,56 g, 100%).

El aceite se disolvió en una solución de NaOH 0,3 M en MeOH/H_2O 1:1 (6 ml) y se agitó una noche a temperatura ambiente. La mezcla de reacción se repartió entre H_2O e IPE. La capa acuosa se acidificó con HCl 1 N y se extrajo con EtOAc. Las capas orgánicas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron para dar el producto (0,45 g, 90% de rendimiento). ^1H RMN (400 MHz, $CDCl_3$): δ 1,39-1,71 (m, 8H), 1,81-1,87 (m, 8H), 2,10-2,15 (m, 1H), 2,59-2,68 (m, 2H), 3,51 (s, 2H), 3,75 (s, 2H), 7,11 (dd, J = 8,1Hz, 1,8), 7,27 (d, J = 1,8 Hz, 1H), 7,37 (d, J = 8,1Hz, 1H). ESIMS (MH+): 388.



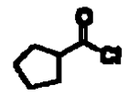
Ejemplo C(17): Ácido 3-ciclopentil-3-hidroxipent-4-enoico



Una solución de NaOH (30 g en 300 ml agua, 0,75 mol) se añadió a una mezcla de 3-ciclopentil-3-hidroxipent-4-enoato de metilo (74 g, 0,37 mol, de la etapa 4 mostra-

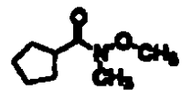
da a continuación) en metanol (300 ml) a 15 °C. Después de la adición, la mezcla se agitó a temperatura ambiente durante una noche. Se retiró el metanol y la solución acuosa se extrajo con Et_2O (200 ml x 2) y acetato de etilo (200 ml x 2) para retirar las impurezas neutras. La fase acuosa se acidificó a pH=2 con HCl 4 N y se extrajo con CH_2Cl_2 (200 ml x 2 + 100 ml). Las capas orgánicas combinadas se lavaron con agua y salmuera y se secaron sobre Na_2SO_4. Después de la evaporación, el compuesto bruto obtenido se re-cristalizó en hexano (aproximadamente 100 ml) para producir 44,3 g de producto puro y se recuperaron 7 g de material bruto. ^1H RMN (300 MHz, $CDCl_3$): δ 1,26-1,69 (m, 8H), 1,99-2,08 (m, 1H), 2,60 (d, J = 15,6, 1H), 2,68 (d, J = 15,6, 1H),5,17-5,33 (m, 2H),5,82-5,92 (m, 1H). ESIMS (MH-): 183.

Etapa 1: Cloruro de ciclopentanocarbonilo



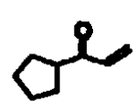
Se disolvió ácido ciclopentano carboxílico (100 g) en 250 ml de $SOCl_2$ y se calentó a reflujo durante aproximadamente 3 h. El exceso de $SOCl_2$ se retiró a presión reducida. El cloruro de ácido se obtuvo mediante la destilación a alto vacío (102 g).

Etapa 2: N-Metoxi-N-metilciclopentanocarboxamida



Se añadió gota a gota cloruro de ciclopentano carbonilo (65 g, 0,49 mol) a una mezcla de Et_3N (180 ml, 1,3 mol) e hidrocloruro de N,O-dimetil hidroxilamina (50 g, 0,52 mol) en CH_2Cl_2 anhidro a 0 °C. Después de la adición, la mezcla de reacción se dejó en agitación a temperatura ambiente durante una noche. A la mezcla de reacción se le añadieron aproximadamente 100 g de hielo picado seguido de 100 g de agua. La mezcla se separó y la capa acuosa se extrajo con CH_2Cl_2 (100 ml x 2). Las capas orgánicas combinadas se lavaron con HCl 1 N, agua y salmuera y se secaron sobre Na_2SO_4. El disolvente se retiró a presión reducida para producir 61 g del producto deseado en forma de un aceite con un rendimiento de 78,8%.

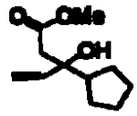
Etapa 3: 1-Ciclopentil-propenona



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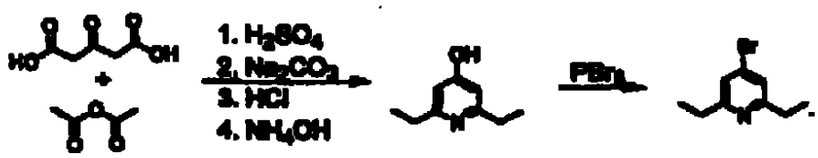
A una solución de N-metoxi-N-metilciclopentanocarboxamida (40 g, 0,25 mol) en 200 ml of THF anhidro se le añadió gota a gota una solución de bromuro de vinilmagnesio (solución 1,0 M en THF, 300 ml, 0,3 mol) a -30 °C y en una atmósfera de nitrógeno. la mezcla de reacción después se agitó a temperatura ambiente durante una noche. La reacción se interrumpió por la adición de anhídrido acético (48 ml) seguido de metanol (48 ml). La solución se concentró a presión reducida y se añadieron 300 ml de éter seguido de 300 ml de HCl 1 N. La mezcla se separó y la capa acuosa se extrajo con éter (100 ml x 2). Las capas orgánicas se combinaron, se lavaron con agua y salmuera y se secaron sobre Na_2SO_4. Después de la evaporación, se obtuvieron 31 g de compuesto bruto y se usaron en la siguiente etapa sin purificación adicional.

Etapa 4: 3-Ciclopentil-3-hidroxipent-4-enoato de metilo

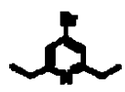


A una suspensión de cinc activado (27 g, 0,4 mol) en éter etílico anhidro (200 ml) se le añadió gota a gota una solución de bromoacetato de metilo (24 ml, 0,24 mol) y 1-ciclopentil-propenona (31 g, 0,24 mol) en 100 ml de éter etílico anhidro. Una vez comenzada la reacción, se añadió el resto de la solución a una velocidad tal como para permitir un reflujo suave. Cuando se completó la adición, la mezcla se calentó a reflujo durante 3 h más. La mezcla se enfrió y se inactivó con AcOH acuoso al 10%. El exceso de cinc se retiró por filtración. El filtrado se trató con cloruro amónico saturado. La capa de éter se separó y la fase acuosa se extrajo con éter (100 ml x 2). Los extractos combinados se lavaron con agua y salmuera, se secaron sobre Na_2SO_4 y se concentraron para dar el producto (36,4 g).

Ejemplo (C18): 4-Bromo-2,6-dietil-piridina



4-Bromo-2,6-dietil-piridina



Se disolvió 2,6-dietil-piridin-4-ol de la etapa 1 mostrada a continuación (4 g, 26,45 mol) en $CHCl_3$ (40 ml) y PBr_5 (11,43 g, 26,45 mmol). La reacción se calentó a 60

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°C durante 1 hora y se evaporó el $CHCl_3$. El residuo se calentó a 120 °C durante 8 horas. Después de enfriar, la mezcla de reacción se añadió cuidadosamente con una solución hecha con agua (500 ml) y gránulos de NaOH (45 g), y después se extrajo 3 veces con EtOAc (100 ml). Las capas orgánicas combinadas se secaron sobre sulfato sódico y se concentraron hasta dar un aceite de color pardo que se purificó a través de un lecho corto de gel de sílice con EtOAc al 10%/hexanos (x 1000 ml).

Etapa 1: 2,6-Dietil-piridin-4-ol

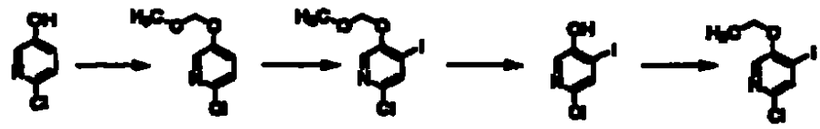


Se añadió rápidamente ácido acetonadicarboxílico (Aldrich, 165115) (60 g, 0,41 mol) a anhídrido propiónico (Aldrich, 240311) (170 ml, 1,3 mol) que contenía ácido sulfúrico concentrado (2 ml) y la mezcla de reacción se calentó a 100 °C durante 30 minutos con agitación. La solución se enfrió rápidamente en una mezcla de hielo-sal y justo cuando se estaba formando un sólido blanco, la reacción añadió a agua fría (500 ml), se agitó y se filtró inmediatamente. El producto se secó al aire y se puso en un matraz de 3 litros y se trató con carbonato sódico acuoso al 10% (600 ml). La pasta resultante se agitó con un agitador y se calentó a 100 °C durante 30 min. Se desprendió dióxido de carbono y se obtuvo una solución de color amarillo claro que se calentó a 85-90 °C durante 80 minutos más. La solución se enfrió y se acidificó con ácido acético acuoso al 30% hasta que no se desprendió más dióxido de carbono. El precipitado blanco se filtró, se lavó con agua, se secó al aire y después se añadió a ácido clorhídrico concentrado (120 ml) en un matraz de fondo redondo de 2 litros y la mezcla se calentó a reflujo durante 4 horas. La solución se enfrió en hielo y se neutralizó por la adición de una solución agitada de carbonato sódico (aproximadamente 115 g) en agua (aproximadamente 500 ml). La solución neutra se extrajo minuciosamente con EtOAc. El extracto se secó y se retiró del disolvente para dar el producto, 2,6-dietil-4-pirona, en forma de un aceite de color pardo. (Yates et al, JOC, vol. 34, No, 12, 1969, páginas 4046-4052)

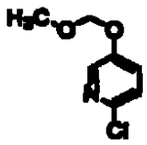
El producto anterior se disolvió en NH_3 al 28% en H_2O (10 equivalentes) y la reacción se calentó a 50 °C durante una noche. A la mañana siguiente, los disolventes se retiraron completamente para producir el compuesto del título en forma de un aceite de color pardo, que se sometió en bruto a una reacción de bromación.

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Ejemplo (C19): 2-Cloro-5-etoxi-4-yodo-piridina



Etapa 1: 2-Cloro-5-metoximetoxi-piridina



Se suspendió hidruro sódico (dispersión en aceite al 60 %, 1,83 g, 46,0 mmol) DMF anhidra (50 ml) en una atmósfera de N_2 a temperatura ambiente con agitación. Se añadió gota a gota durante 30 minutos una solución de 2-cloro-5-hidroxi-piridina (5,0 g, 38,2 mmol) en DMF anhidra (20 ml). Se continuó agitando a temperatura ambiente durante 1,5 horas. Después se añadió clorometil metil éter (3,32 ml, 44,1 mmol) puro durante 20 min. Se continuó agitando a temperatura ambiente durante 12 horas. La mezcla se repartió entre agua y EtOAc. Los extractos orgánicos se lavaron con salmuera, se secaron sobre Na2SO4, se filtraron y se concentraron. El residuo bruto se cromatografió sobre gel de sílice, eluyendo con EtOAc al 20% en hexanos para proporcionar el producto deseado en forma de un aceite transparente (6,4 g, 96%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,18 (s, 1H), 7,36 (d, J = 8,6 Hz, 1H), 7,23 (d, J = 8,6 Hz, 1H),5,19 (s, 2H), 3,50 (s, 3H).

Etapa 2: 2-Cloro-4-yodo-5-metoximetoxi-piridina

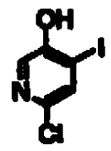


Se disolvió 2-cloro-5-metoximetil-piridina (1 g,5,8 mmol) en THF anhidro (30 ml) y se enfrió a -78 °C con agitación magnética en una atmósfera de N_2. Después, se añadió t-BuLi (1,7M en pentano (5,76 ml, 11,5 mmol) durante 10 minutos. La solución parda resultante se dejó en agitación a -78 °C durante 30 min. Se añadió gota a gota yodo durante 20 minutos (2,19 g, 8,6 mmol) como una solución en THF (15 ml). La mezcla se agitó a -78 °C durante 1 hora. La reacción se interrumpió a -78 °C con agua y se dejó calentar a temperatura ambiente. La mezcla se repartió entre EtOAc y agua. La fase acuosa se extrajo con EtOAc (2 x 100 ml). Los extractos orgánicos combinados se lavaron con tiosulfato sódico acuoso saturado (2 x 100 ml) y salmuera (100 ml). Los extractos orgánicos se secaron sobre Na2SO4, se filtraron y se concentraron. El resi-

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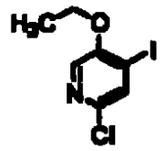
duo amarillo/naranja se trituró con hexanos para proporcionar un sólido amarillo (0,88 g,51%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,09 (s, 1H), 7,75 (s, 1H),5,25 (s, 2H), 3,50 (s, 3H).

Etapa 3: 6-Cloro-4-yodo-piridin-3-ol



Se disolvió 2-cloro-4-yodo-5-metoximetoxi-piridina (0,6 9, 2,7 mmol) en THF (4 ml) y HCl 3 N (6 ml). La mezcla se calentó a 60 °C con agitación magnética. Se mantuvo el calentamiento durante 3 horas. La mezcla se enfrió a temperatura ambiente y el pH se ajustó a 7 con la adición lenta de bicarbonato sódico acuoso saturado. El producto resultante se extrajo con EtOAc (3 x 50 ml), se secó sobre Na_2SO_4, se filtró y se concentró. El sólido se suspendió en EtOAc y se agitó durante 12 horas a temperatura ambiente. La mezcla se filtró y el filtrado se concentró para producir un sólido blanquecino (0,63 g, 93%). ^{1}H RMN (400 MHz, DMSO-d6): δ 11,10 (s a, 1H), 7,89 (s, 2H).

Etapa 4: 2-Cloro-5-etoxi-4-yodo-piridina



Se disolvió 6-cloro-4-yodo-piridin-3-ol (0,419, 1,62 mmol) en DMF anhidra (4 ml) y se agitó a temperatura ambiente. Se añadieron secuencialmente carbonato potásico (0,67 g, 4,9 mmol) y yodoetano (0,40 ml, 4,9 mmol). La mezcla se calentó a 60 °C y se mantuvo durante 2 horas. La mezcla se enfrió a temperatura ambiente y se filtró. El filtrado se diluyó con éter dietílico (25 ml) y se lavó con ácido cítrico acuoso al 20% (25 ml). La capa acuosa se extrajo con éter dietílico (2 x 20 ml). Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo se trituró con hexano, dando como resultado un sólido castaño (0,42 g, 91%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,80 (s, 1H), 7,74 (s, 1H) 4,18 (q, J = 7,1Hz, 2H), 1,51 (t, J = 7,1Hz, 3H).

<u>Ejemplo D1:</u> Actividad Antiviral

Se ensayó la actividad con la polimerasa de HCV de los compuestos descritos

en este documento. Se ensayó la capacidad de la polimerasa de HCV recombinante de realizar una transcripción dirigida por cebador/plantilla en ensayos que contenían tris-HCl 30 mM pH 7,2, $MgCl_2$ 10 mM, NaCl 20 mM, Ditiotreitol (DTT)1 mM Tween-20 al 0,05%, glicerol al 1%,5 pmoles de biotina-dG_{12} (cebador), 0,5 pmoles de poli(rC)$_{300}$ (plantilla), GTP 1 µM, 0,1-0,3 uCi de α-^{33}P-GTP y 2,5 pmoles (0,15 µg) de proteína polimerasa de HCV en un volumen final de 75 µl. Las reacciones se iniciaron por la adición de enzima y se incubaron durante 30 minutos a 30°C. Las reacciones se interrumpieron por la adición de EDTA 33 mM y se recogieron productos polinucleotídicos por filtración a través de papeles de dietilaminoetilo (DE) Filtermat (Wallac). El trifosfato no incorporado se retiró lavado los filtros con fosfato sódico dibásico al 5%. Los filtros se contaron en un contador de centelleo Packard Tri-Lux Microbeta (Packard Bioscience, Meriden, CT). Los compuestos a ensayar se añadieron a diversas concentraciones, por ejemplo, de 1 µM a 50 µM, desde soluciones madre en DMSO al 10%-agua (el DMSO final está al 1% en la reacción).

Se estimaron los valores de CI_{50} a partir de los datos de cpm primarios (recogidos por triplicado) usando la fórmula: cpm (I)= cpm (sin inhibidor)(1- ([1]/([1] + IC_{50}))). Un valor de CI_{50} representa la concentración (en µM) de un compuesto que proporciona una inhibición de 50% de la transcripción dirigida por la polimerasa en el ensayo anterior. Se expresó un valor en porcentaje para un compuesto cuando era poco práctico calcular un valor de CI_{50} con los datos disponibles. Cuando la CI_{50} estimada por la ecuación anterior fue menor de 200 nM, se volvió a calcular usando la siguiente ecuación, que tiene en cuenta la concentración de enzima (30 nM) en el ensayo: cpm(I) = cpm(sin inhibidor)(1-((((I+IC_{50}+30e-9)-sqrt(((I+IC_{50}+30e-9)^2)-4 x 30e-9 x I)))/((2) (30e-9))). El ajuste de la curva se realizó usando el programa KaleidaGraph (Synergy Software, Reading, Pennsylvania).

En la Tabla 1 mostrada a continuación se presentan los datos de concentración de inhibición (IC_{50}) para compuestos ilustrativos de la invención.

Tabla 1

Ejemplo Nº	CI50 (µM)
A(1)	0,003
A(101)	0,008
A(111)	0,005
A(116)	0,005
A(117)	0,005
A(12)	0,002
A(21)	0,001
A(22)	0,004

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A(23)	0,006
A(13)	0,001
A(24)	0,014
A(26)	0,004
A(30)	0,004
A(31)	0,006
A(37)	0,003
A(47)	0,005
A(49)	0,007
A(50)	0,004
A(57)	0,003
A(58)	0,001
A(59)	0,003
A(74)	0,003
A(75)	0,005
A(76)	0,005
A(77)	0,005
A(78)	0,012
A(84)	0,072
A(85)	0,083
A(86)	0,086
A(89)	0,009
A(94)	0,027
A(95)	0,04
A(96)	0,006
A(97)	0,011
B(14)	0,026
B(18)	0,17
B(19)	1,1
B(20)	0,005
B(22)	0,042
B(23)	0,14
B(24)	0,1
B(25)	0,033
B(28)	0,005
A(28)	0,002
A(79)	0,012
A(103)	0,003
A(104)	0,006
A(106)	0,004
A(107)	0,006
A(108)	0,006
A(109)	0,006
A(114)	0,005
A(115)	0,006
A(118)	0,007
A(119)	0,01
A(120)	0,007
A(121)	0,006
A(125)	0,01
A(126)	0,006
A(127)	0,13
A(128)	0,006

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A(129)	0,004
A(130)	0,003
A(131)	0,002
A(132)	0,035
A(133)	0,005
A(19)	0,012
A(20)	0,009
A(25)	0,1
A(29)	0,017
A(64)	
A(65)	0,25
A(69)	0,015
A(70)	0,014
A(71)	0,009
A(72)	0,008
A(80)	0,022
A(81)	0,12
A(82)	0,065
A(83)	0,038
A(91)	0,16
A(92)	0,3
A(98)	0,011
B(1)	0,06
B(11)	0,26
B(12)	0,11
B(32)	0,091
B(33)	0,028
B(35)	0,01
B(36)	0,019
B(37)	0,022
B(38)	0,067
B(4)	0,006
B(8)	0,029
B(9)	0,006
A(102)	0,84
A(105)	0,25
A(135)	0,21
A(37)	6,6
A(63)	18,5
A(66)	31
A(67)	47
A(68)	12
A(73)	19% inh @ 50uM
A(88)	27
A(90)	43
A(99)	8,4
B(10)	30
B(2)	48
B(3)	6,4
B(34)	1,3
B(5)	22
B(6)	12

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B(7)	7
A(10)	0,003
A(11)	0,008
A(124)	0,008
A(14)	0,008
A(15)	0,007
A(16)	0,055
A(17)	0,016
A(18)	0,17
A(2)	0,62
A(27)	0,003
A(3)	0,001
A(33)	0,007
A(34)	0,012
A(35)	0,009
A(36)	0,03
A(38)	0,003
A(39)	0,006
A(4)	0,007
A(40)	0,012
A(41)	0,008
A(42)	0,004
A(43)	0,008
A(44)	0,007
A(45)	0,014
A(46)	0,006
A(48)	0,023
A(5)	8,6
A(51)	0,003
A(52)	0,003
A(53)	0,003
A(54)	0,003
A(55)	0,002
A(56)	0,004
A(6)	0,039
A(61)	0,14
A(62)	0,06
A(7)	11,3
A(8)	0,099
A(9)	0,005
B(29)	5,2
B(30)	1,2
B(31)	0,18
B(39)	0,012
A(100)	0,079
A(110)	0,006
A(112)	0,007
A(113)	0,007
A(122)	0,004
A(123)	0,039
A(134)	0,003
A(136)	0,003
A(137)	0,3

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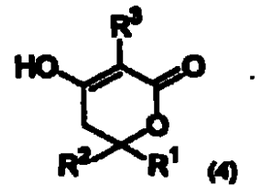
A(138)	0,01
A(139)	0,004
A(32)	0,005
A(60)	0,003
A(93)	0,006
B(13)	0,004
B(15)	0,019
B(16)	0,053
B(17)	0,026
B(21)	0,178
B(26)	18
B(27)	10
B(50)	0,043
B(51)	0,024
A(156)	0,005
A(157)	0,01
A(154)	0,011
A(155)	0,054

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REIVINDICACIONES:

1. Un compuesto de fórmula (4),



(4)

en la que:

R^1 es ciclopentilo;

R^2 es -$(CR^6R^7)_n$(heterociclilo de 5 a 6 miembros), donde dicho grupo heterocíclico de 5 a 6 miembros está opcionalmente sustituido con al menos un grupo R^4;

R^3 es -$(CR^6R^7)_t$(arilo C_6-C_{10}) o -$(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros), estando cada uno de dichos restos arilo C_6-C_{10} y heterociclilo de 4 a 10 miembros de dichos grupos R^3 opcionalmente sustituidos con al menos un grupo R^5;

cada R^4 se selecciona independientemente entre halo, -OR^6, oxo, -NR^6R^7, -CF_3, -CN, -$C(O)R^6$, -$C(O)OR^6$, -$OC(O)R^6$, -$NR^6C(O)R^7$, -$NR^6C(O)OR^7$, -$NR^6C(O)NR^6R^7$, -$C(O)\ NR^6R^7$, -$SO_2\ NR^6R^7$, -NR^6SO2R^7, alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6, donde dichos grupos alquilo C_1-C_6, alquenilo C_2-C_6 y alquinilo C_2-C_6 están opcionalmente sustituidos con al menos un R^5;

cada R^5 se selecciona independientemente entre alquilo C_1-C_6, halo, -OR^6, -CF_3 y -CN;

cada uno de R^6 y R^7 se selecciona independientemente entre hidrógeno y alquilo C_1-C_6;

n es 0, 1, 2, 3, 4, ó 5; y

t es 0, 1, 2, 3, 4, ó 5; o

sales farmacéuticamente aceptables o solvatos de los mismos, con la condición de que el compuesto de fórmula (4) no sea 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-ilmetil]-6-[2-(2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, 3-[(6-cloro[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-ciclopentil-6-[2-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona, o 6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil-6-[2-(5-etilpiridin-3-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona.

2. Un compuesto de acuerdo con la reivindicación 1, donde n es 1 ó 2; y t es 1 ó 2.

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3. Un compuesto de acuerdo con la reivindicación 2, donde n es 2.

4. Un compuesto de acuerdo con la reivindicación 3, donde R^3 es -$(CR^6R^7)_t$(heterociclilo de 4 a 10 miembros), opcionalmente sustituido con al menos un grupo R^5.

5. Un compuesto de acuerdo con la reivindicación 4, donde t es 1.

6. Un compuesto de acuerdo con la reivindicación 5, donde R^2 es un grupo -$(CH_2)_2$(piridilo), -$(CH_2)_2$(pirazolilo), -$(CH_2)_2$(pirrolilo), -$(CH_2)_2$(oxazolilo), -$(CH_2)_2$(tiazolilo), -$(CH_2)_2$(imidazolilo), -$(CH_2)_2$(isoxazolilo), -$(CH_2)_2$(isotiazolilo), -$(CH_2)_2$(1,2,3-triazolilo), -$(CH_2)_2$(1,3,4-triazolilo), $(CH_2)_2$(1,3,4-tiadiazolilo), -$(CH_2)_2$(piridazinilo), -$(CH_2)_2$(pirimidinilo), -$(CH_2)_2$(pirazinilo), o -$(CH_2)_2$(1,3,5-triazinilo), cada uno de los cuales está opcionalmente sustituido con al menos un grupo R^4.

7. Un compuesto de acuerdo con la reivindicación 6, donde R^3 es -(CH_2)([1,2,4]triazolo[1,5-a]pirimidin-2-ilo), opcionalmente sustituido con al menos un grupo R^5.

8. Un compuesto de acuerdo con la reivindicación 7, donde R^2 es -$(CH_2)_2$(piridilo), -$(CH_2)_2$(pirazolilo), o -$(CH_2)_2$(pirrolilo), cada uno de los cuales está opcionalmente sustituido con al menos un grupo R^4.

9. Un compuesto de acuerdo con la reivindicación 8, donde R^2 es -$(CH_2)_2$(piridilo) o -$(CH_2)_2$(pirazolilo), cada uno de los cuales está opcionalmente sustituido con al menos un grupo R^4.

10. Un compuesto de acuerdo con la reivindicación 9, donde:

R^2 es -$(CH_2)_2$(piridilo) o -$(CH_2)_2$(pirazolilo), cada uno de los cuales está opcionalmente sustituido con al menos un sustituyente seleccionado entre halo, alquilo C_1-C_6, -OR^6, oxo y -NR^6R^7; y

R^3 es -(CH_2)([1,2,4]triazolo[1,5-a]pirimidin-2-ilo), opcionalmente sustituido con al menos un sustituyente seleccionado entre halo y alquilo C_1-C_6.

11. Un compuesto de acuerdo con la reivindicación 10, donde R^2 es -$(CH_2)_2$(piridilo)

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opcionalmente sustituido con al menos un sustituyente seleccionado entre halo, alquilo C_1-C_6, $-OR^6$ y $-NR^6R^7$.

12. Un compuesto según la reivindicación 1, seleccionado entre:

6-[2-(6-amino-5-etil-2-metilpiridin-3-il)etil]-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(4-etilpiridin-2-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(4-etilpiridin-2-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(2,6-dietilpiridin-4-il)etil]-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(2,6-dimetilpiridin-4-il)etil]-3-[(5,7-dimetil[1,2,4]triazolo-[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo(1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-metoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-[2-(2-isopropilpiridin-4-il)etil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-6-isopropilpiridin-4-il)etil)-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-6-metilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(2,6-dietilpiridin-4-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(2-etil-5-metoxipiridin-4-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-propoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-ciclopentil-6-[2-(2-etil-5-propoxipiridin-4-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;

6-(2-[2,6-bis(2,2,2-trifluoroetil)piridin-4-il]etil)-6-ciclopentil-4-hidroxi-3-((6-

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metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona;
6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(6-etil-3-metoxipiridin-2-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(1-etil-1H-pirazol-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-[2-(1-isopropil-1H-pirazol-4-il)etil]-5,6-dihidro-2H-piran-2-ona;
6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-[2-(5-metoxi-2-metilpiridin-4-il)etil]-5,6-dihidro-2H-piran-2-ona;
6-{2-[2,6-bis(2,2,2-trifluoroetil)piridin-4-il]etil}6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
5-bromo-1-(2-2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)piridin-2(1H)-ona;
1-(2-{2-ciclopentil-5-[(5, 7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)-5-etilpiridin-2(1H)-ona;
2-[3-cloro-5-(2-(2-ciclopentil-5-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-6-oxo-3,6-dihidro-2H-piran-2-il}etil)piridin-2-il]-2-metilpropanonitrilo;
(+)-6-{2-[2,6-bis(2,2,2-trifluoroetil)piridin-4-il]etil}6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(-)-6-{2-[2,6-bis(2,2,2-trifluoroetil)piridin-4-il]etil}6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(+)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-metoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(-)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-metoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(+)-6-ciclopentil-6-[2-(2,6-dietilpiridin-4-il)etil]-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(-)-6-ciclopentil-6-[2-(2,6-dietilpiridin-4-il)etil]-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(+)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(-)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(+)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-propoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;

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(-)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-propoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(+)-6-ciclopentil-6-[2-(5-etoxi-2-etilpiridin-4-il)etil-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona; y
(-)-6-ciclopentil-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona; o
sus sales o solvatos farmacéuticamente aceptables.

13. Un compuesto según la reivindicación 1, seleccionado entre:
(+)-6-{2-[2,6-bis(2,2,2-trifluoroetil)piridin-4-il]etil}6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(-)-6-{2-[2,6-bis(2,2,2-trifluoroetil)piridin-4-il]etil}6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(+)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-metoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(-)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-metoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(+)-6-ciclopentil-6-[2-(2,6-dietilpiridin-4-il)etil]-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(-)-6-ciclopentil-6-[2-(2,6-dietilpiridin-4-il)etil]-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(+)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(-)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(+)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-propoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(-)-6-ciclopentil-3-[(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-6-[2-(2-etil-5-propoxipiridin-4-il)etil]-4-hidroxi-5,6-dihidro-2H-piran-2-ona;
(+)-6-ciclopentil-6-[2-(5-etoxi-2-etilpiridin-4-il)etil-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona; y
(-)-6-ciclopentil-6-[2-(5-etoxi-2-etilpiridin-4-il)etil]-4-hidroxi-3-[(6-metil[1,2,4]triazolo[1,5-a]pirimidin-2-il)metil]-5,6-dihidro-2H-piran-2-ona; o
sus sales y solvatos farmacéuticamente aceptables.

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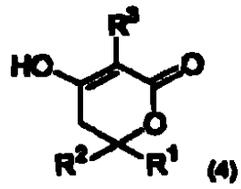
14. Una composición farmacéutica, que comprende una cantidad terapéuticamente eficaz de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 13 y un vehículo farmacéuticamente aceptable.

15. Un uso de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 13 en la preparación de un medicamento para el tratamiento de un mamífero que padece infección por el virus de la Hepatitis C.

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RESUMEN

La presente invención proporciona compuestos de fórmula (4) y sus sales farmacéuticamente aceptables y solvatos, que son útiles como inhibidores de la enzima polimerasa del virus de la Hepatitis C (HCV) y también son útiles para el tratamiento de infecciones por HCV en mamíferos infectados por HCV. La presente invención también proporciona composiciones farmacéuticas que comprenden compuestos de fórmula (4), sus sales farmacéuticamente aceptables y solvatos. Además, la presente invención proporciona compuestos intermedios y métodos útiles en la preparación de compuestos de fórmula (4).



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TRATAD DE COOPERACIÓN DE PATENTES
PCT
NOTIFICACIÓN DE TRANSMISIÓN DEL REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL DE PATENTABILIDAD
(PCT Regla 71.1)
De: AUTORIDAD DE REVISION PRELIMINAR INTERNACIONAL

Para:
RUDDOCK, Keith, S.
c/o Pfizer Research and Development
Ramsgate Road
Kent
Sándwich CT13 9NJ
Gran Bretaña

Sello de Recibido 17 de julio de 2006 Departamento de patentes

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Referencia del expediente del solicitante o mandatario: PC32310A
Solicitud Internacional No.: PCT/IB2005/002697
Fecha de presentación internacional: 05.08.2005
Fecha de prioridad: 18.08.2004
Solicitante: PFIZER INC. et al

1. Se notifica al solicitante que la Administración Encargada del Examen Preliminar Internacional ha emitido el informe de examen preliminar internacional para la solicitud internacional y se lo transmite adjunto, acompañado, si procede, de sus anexos.

2. Se transmite una copia del presente informe y, si procede, de sus anexos, a la Oficina Internacional para comunicación a todas las Oficinas elegidas.

3. Si alguna Oficina elegida lo exige, la Oficina Internacional realizará una traducción en inglés del informe (con exclusión de sus anexos) y la transmitirá a las Oficinas interesadas.

4. **RECORDATORIO**

Para iniciar la fase nacional ante cada Oficina elegida, el solicitante debe cumplir ciertos actos (presentación de la traducción y pago de las tasas nacionales) en el plazo de 30 meses desde la fecha de prioridad (o más tarde por lo que respecta a ciertas oficinas) (Artículo 39 (1)) (véase también el recordatorio enviado por la Oficina Internacional en el formulario PCT/IB/301).

Cuando deba entregarse una traducción de la solicitud internacional o una oficina elegida, se incluirá la traducción de cualquier anexo de

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informe de Examen Preliminar Internacional. Corresponde al solicitante preparar la traducción en cuestión y entregarla directamente a cada Oficina elegida interesada

Para más amplios detalles en lo relativo a los plazos aplicables y las exigencias de las oficinas elegidas, véase el Volumen II de la guía del solicitante PCT.

Se llama la atención del solicitante sobre el Artículo 33(5) que prevé que los criterios de novedad, actividad inventiva y de aplicación industrial definidos en el Artículo 33(2) a (4) sólo servirán a los efectos del examen preliminar internacional, y que "todo Estado contratante puede aplicar criterios adicionales o diferentes al objeto de decidir, en ese Estado, si la invención es patentable o no" (véase también el Artículo 27(5)). Tales criterios adicionales pueden afectar, por ejemplo, a las excepciones de patentabilidad, requisitos específicos relativos a la divulgación, la claridad de las reivindicaciones.

Nombre y dirección postal de la Administración encargada del Examen Preliminar Internacional:

Oficina de Patentes Europea
D- 80298 Munich
Tel: +49-89 2399- 0 Tx: 523656 epmu d
Fax: +49 89 2399 – 4465

Funcionario Autorizado: Brell, E
Tel: + 49 89 2399-6724

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TRATADO DE COOPERACIÓN DE PATENTES
PCT
INFORME PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD
(Capítulo II del Tratado de Cooperación en materia de Patentes)
(PCT Artículo 36 y Regla 70)

Referencia del expediente del solicitante o mandatario: PC32310A
Solicitud Internacional No.: PCT/IB2005/002697
Fecha de presentación internacional: 05.08.2005
Fecha de prioridad: 18.08.2004
Clasificación Internacional de Patentes (IPC) o la vez clasificación nacional e IPC: INV. CO7D487/04 CO7D405/06 CO7D309/32 CO7D513/04 CO7D405/14 A61K31/351 A61K31/366 A61P31/14
Solicitante: PFIZER INC et al

1. El reporte de examen preliminar internacional ha sido preparado por esta Autoridad de Revisión Preliminar Internacional bajo el Artículo 35 y es transmitido al solicitante según el Artículo 36.

2. Este REPORTE consta de un total de 5 hojas, incluida la presente hoja de portada.

3. Este informe también contiene ANEXOS, que comprenden.

   a. ☐ (*remitido al solicitante y a la oficina internacional*) un total de ___ hojas, descritas a continuación:

      ☐ hojas de la descripción, las reivindicaciones y/o los dibujos que han sido modificadas y que sirven de base al presente informe, y/o de hojas que contienen rectificaciones autorizadas por esta Administración (véase la Regla 70.16 y la Instrucción Administrativa 607 del PCT).

      ☐ hojas que reemplazan a otras hojas anteriores, pero que esta Administración considera que contienen modificaciones que se extienden más allá de la divulgación de la invención tal como fue originalmente presentada, según se indica en el punto 4 del Reglamento I y en el Recuadro Suplementario.

   b. ☐ (remitido únicamente a la Oficina Internacional) un total de (indicar tipo y soporte(s) electrónico(s)) , que contienen una lista de secuencias y/o tabla(s) relativa(s), solo en formato legible por ordenador, como se indica en el Recuadro Suplementario relativo a Listas de Secuencias (ver Instrucción Administrativa 802).

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4. El presente informe contiene indicaciones relativas a los siguientes puntos:

☒	Recuadro I	Base de este informe
☐	Recuadro II	Prioridad
☐	Recuadro III	Ninguna formulación de opinión sobre la novedad, la actividad inventiva y la aplicación industrial
☐	Recuadro IV	Falta de unidad de Invención
☒	Recuadro V	Declaración motivada según el Artículo 35(2) sobre la novedad, la actividad inventiva y la aplicación industrial, citas y explicaciones en apoyo de esta declaración
☒	Recuadro VI	Ciertos documentos citados
☐	Recuadro VII	Defectos en la Solicitud Internacional
☒	Recuadro VIII	Observaciones relativas a la solicitud internacional

Fecha de radicación de la demanda: 06.10.2005
Fecha de elaboración de este reporte: 14.07.2006

Nombre y dirección postal de la Administración encargada del Examen Preliminar Internacional:

Oficina de Patentes Europea
D- 80298 Munich
Tel: +49-89 2399 – Tx: 523656 epmu d – 0
Fax: +49-89 2399 – 4465

Funcionario Autorizado: Fazzi, R
Tel: + 49 89 2399-

Recuadro I. Base de este informe

1. Por lo que respecta al **idioma**, este informe se ha establecido sobre la base de la solicitud internacional en el idioma en el cual se depositó, salvo indicación en contra señalada a continuación.

☐ Este informe está basado en una traducción del idioma original al siguiente idioma , que es el de una traducción proporcionada a los fines de:
- ☐ búsqueda internacional (según Reglas 12.3 y 23.1 (b))
- ☐ publicación de la solicitud internacional (según Regla 12.4)
- ☐ examen preliminar internacional (según Reglas 55.2 y/o 55.3)

2. Por lo que respecta a los **elementos*** de la solicitud internacional, esta opinión se ha establecido sobre la base de (*las hojas de reemplazo que hayan sido enviadas a la Oficina receptora en respuesta a un requerimiento según el Artículo 14 se las denomina en este informe como "inicialmente presentadas" y no se anexan al informe):*

Descripción, Páginas

1 – 307 tal como se presentaron inicialmente

Reivindicaciones, Números

1 – 15 tal como se presentaron inicialmente

☐ una lista de secuencias y/o tabla(s) relativa(s) – ver Recuadro Suplementario relativo a Listas de Secuencias

3. ☐ Las modificaciones ha ocasionado la cancelación de:

- ☐ la descripción, páginas
- ☐ las reivindicaciones, Nos.
- ☐ los dibujos, hojas/fig.
- ☐ la lista de secuencias (especificar):
- ☐ tabla(s) relativa(s) a la lista de secuencias (especificar):

4. ☐ El presente informe ha sido establecido como si no se hubiesen presentado (algunas de) las modificaciones anexadas a este informe y listadas abajo, ya que se ha considerado que iban más allá de la divulgación de la invención tal como fue presentada, como se indica en el Recuadro Suplementario (Regla 70.2(c)).

☐ la descripción, páginas
☐ las reivindicaciones, Nos.
☐ los dibujos, hojas/fig.
☐ la lista de secuencias (especificar):
☐ tabla(s) relativa(s) a la lista de secuencias (especificar):

* Si se utiliza el punto 4, algunas o todas estas páginas pueden llevar el sello de "sustituida".

Recuadro No. V Declaración razonada según el Artículo 35 (2) con respecto a la novedad, nivel inventivo o aplicación industrial: anterioridades y explicaciones que soportan tal declaración

1. Declaración

Novedad (N)	Si:	Reivindicaciones 1-15
	No:	Reivindicaciones
Nivel Inventivo (IS)	Si:	Reivindicaciones 1-15
	No:	Reivindicaciones
Aplicación Industrial (IA)	Si:	Reivindicaciones 1-15
	No:	Reivindicaciones

2. Citas y explicaciones (Regla 70.7)

ver hoja separada.

Recuadro No. VI. Ciertos documentos citados

1. Ciertos documentos publicados (Regla 70.10)

y/o

2. Divulgaciones no escritas (Regla 70.9)

Ver hoja adjunta

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Recuadro No. VIII Observaciones relativas a la solicitud internacional.

Se formulan las observaciones siguientes sobre la claridad de las reivindicaciones, de la descripción y de los dibujos o sobre si las reivindicaciones se fundan totalmente en la descripción:

ver hoja adjunta

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL – HOJA ANEXA
Solicitud Internacional No. PCT/IB2005/002697

1) Se hace referencia a los siguientes documentos:

D1: WO 2004/074270 A
D2: WO 03/095441 A

1.1) Con referencia a la sección VI

En vista de su fecha de publicación el 2 de septiembre de 2004, el contenido del antecedente D1 no será utilizado en este Concepto Escrito, pero podría volverse relevante posterior a la entrada de la Fase Europea, si la presente anterioridad se encontrara no válida.

2) La presente solicitud se relaciona con compuestos generales de la fórmula (4) (compare con la reivindicación 1), los cuales son útiles como inhibidores de la enzima HCV (virus de la hepatitis C) polimerasa.

3) Novedad (con referencia a la sección V)

D2 divulga varios compuestos de la fórmula general (I), los cuales sin embargo no poseen el mismo patrón de sustitución de la presente fórmula (4) de la reivindicación 1 (compare con los ejemplos de D2 en comparación con la definición de los presentes sustitutos $R^1 - R^3$).

Por lo tanto, se considera que la materia de las presentes reivindicaciones 1- 15 cumple con los criterios del Artículo 33(2) del PCT.

4) Nivel inventivo (con referencia a la sección V)

El antecedente D2 describe compuestos que contienen una unidad de 5,6- dihidro-piran- 2- ona / piran- 2,4- diona los cuales son inhibidores de la HCV polimerasa ARN-dependiente.
Por lo tanto, el problema a resolverse por la presente solicitud puede plantearse en la necesidad de proveer compuestos similares adicionales para el mismo uso terapéutico.
A partir de las enseñanzas de D2, con el fin de lograr los presentes compuestos, aquella persona capacitada tendría que primero seleccionar una combinación específica de sustitutos, a saber que R_2 es un ciclopentilo no sustituido, y que R_1 y R_3 sean grupos fenilo opcionalmente sustituidos (compare con la definición de la fórmula (I) en la página 5 del antecedente D2).
Adicionalmente, la persona capacitada tendría que cambiar el grupo fenilo de R_1 en D2 en un heterociclo de 5- 6 miembros (compare con la definición del presente sustituto R^2).
En vista de los numerosos cambios entre la presente fórmula (4) y la fórmula (I) de D2, la materia de la presente reivindicación 1 parece no ser obvia con respecto al estado de la técnica más cercano.
Se proporcionan datos para un grupo razonable y representativo de compuestos, los cuales efectivamente soportan la envergadura de la reivindicación principal.

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Por consiguiente, se considera que la materia de las reivindicaciones 1- 15 cumple con los requisitos del Artículo 33(3) del PCT.

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5) Observaciones adicionales (con referencia a la sección VIII)

5.1) Profármaco: no puede buscarse una protección para compuestos especulativos, los cuales todavía necesitan prepararse e investigarse. Aunque existe dentro de la solicitud un indicio con respecto a lo que podría ser, un profármaco no es un término definible con respecto a su estructura. Aquella persona capacitada no tendría indicio alguno en cuanto qué estaría por dentro de su definición, y por lo tanto debería ser removido. Por lo tanto, no se ha llevado a cabo ningún análisis de novedad o nivel inventivo para todos los compuestos que sean combinaciones de "profármaco" y de derivados de la fórmula (4).

5.2) Contrario a los requisitos establecidos por la Regla 5.1(a)(ii) del PCT, no se menciona en la memoria descriptiva el estado de la técnica anterior relevante divulgado en los documentos D1 y D2, ni tampoco se identifican estos documentos en dicha memoria descriptiva.

5.3) La descripción no está en conformidad con las reivindicaciones según es requerido por la Regla 5.1(a)(iii) del PCT.

EUROPEAN PHARMA
PATENT DEPARTMENT
17 JUL 2006

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

RUDDOCK, Keith, S.
c/o Pfizer Research and Development
Ramsgate Road
Kent
Sandwich CT13 9NJ
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing (day/month/year)	14.07.2006
Applicant's or agent's file reference: PC32310A	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/IB2005/002697	05.09.2005	18.09.2004

Applicant
PFIZER INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

FILING	✓
DEBIT NOTE	
RENEWALS	
RECORDABLE	

Name and mailing address of the International preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Brell, E

Tel. +49 89 2399-8724

Form PCT/IPEA/416 (January 2004)

PATENT C OPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC32310A	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/IB2005/002697	International filing date (day/month/year) 05.08.2005	Priority date (day/month/year) 18.08.2004

International Patent Classification (IPC) or national classification and IPC
INV. C07D487/04 C07D405/06 C07D309/32 C07D513/04 C07D405/14 A61K31/551 A61K31/366 A61P31/14

Applicant
PFIZER INC. et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ 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 Article 35(2) 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

Date of submission of the demand	Date of completion of this report
06.10.2005	14.07.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fazzi, R Telephone No. +49 89 2399-

Form PCT/IPEA/409 (Cover Sheet) (April 2005)

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements* of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-307 as originally filed

   Claims, Numbers

   1-15 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT N PATENTABILITY

International application No. PCT/IB2005/002697

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-15
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VII 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

1) Reference is made to the following documents:

D1: WO 2004/074270 A
D2: WO 03/095441 A

1.1) Reference to section VI

In view of its publication date of 2 September 2004, the content of D1 will not be used in this Written Opinion, but it could become relevant after the entrance into the European Phase, if the present priority were found invalid.

2) The present application relates to general compounds of formula (4) (cf. claim 1), which are useful as inhibitors of the Hepatitis C Virus (HCV) polymerase enzyme.

3) Novelty (Reference to section V)

D2 discloses several compounds of general formula (I), which however do not possess the same substitution pattern of present formula (4) of claim 1 (cf. examples of D2 in comparison with the definition of present substituents R^1-R^3).

Thus, the subject-matter of current claims 1-15 is considered to meet the criteria of Article 33(2) PCT.

4) Inventive step (Reference to section V)

D2 describes compounds containing a 5,6-dihydro-pyran-2-one/pyran-2,4-dione unity which are hepatitis C virus RNA-dependent polymerase inhibitors.
Thus, the problem to be solved by the present application may be seen in the provision of further similar compounds for the same therapeutical use.
From the teaching of D2, in order to arrive at present compounds, the skilled person would have first to select a specific combination of subetituents, namely that R_2 is an unsubstituted cyclopentyl, and that R_1 and R_3 are optionally substituted phenyl groups (cf. definition of formula (I) on page 5 of D2).
Further, the skilled person would have to change the phenyl group of R_1 of D2 into a 5-6

membered heterocycle (cf. definition of present R^2 substituent).
In view of the many changes between present formula (4) and formula (I) of D2, the subject-matter of present claim 1 seems to be non-obvious over the closest state of the art.
Data are given for a reasonable and representative group of compounds, which indeed supports the breadth of the main claim.

Thus, the subject-matter of claims 1-15 is considered to meet the requirements of Article 33(3) PCT.

5) Further observations (Reference to section VIII)

5.1) Prodrug: protection cannot be sought for speculative compounds, which have yet to be prepared and investigated. Although there is an indication within the application as to what it may be, a prodrug is not a definable term as regards its structure. The skilled person has no indication as to what falls within this definition, and it should thus be deleted. No analysis of novelty and inventive step has therefore been made for all the compounds which are combinations of "prodrug" and of derivatives of formula (4).

5.2) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.

5.3) The description is not in conformity with the claims as required by Rule 5.1(a)(iii) PCT.

INTERNATIONAL SEARCH REPORT

Inter ...nal Application No
PCT/IB2005/002697

A. CLASSIFICATION OF SUBJECT MATTER
C07D487/04 C07D405/06 C07D309/32 C07D513/04 C07D405/14
A61K31/351 A61K31/366 A61P31/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, 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.
P,X	WO 2004/074270 A (PFIZER INC; BORCHARDT, ALLEN, JOHN; GONZALEZ, JAVIER; LI, HUI; LINTON,) 2 September 2004 (2004-09-02) examples 162,164,275	1-15
X	WO 03/095441 A (PFIZER INC; GONZALEZ, JAVIER; BORCHARDT, ALLEN, JOHN; DRABOWICH, PETER) 20 November 2003 (2003-11-20) examples	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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
7 December 2005	22/12/2005

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fazzi, R

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/IB2005/002697

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004074270 A	02-09-2004	AU 2004213247 A1	02-09-2004
		CA 2516235 A1	02-09-2004
		EP 1597246 A2	23-11-2005
		NL 1025544 A1	24-08-2004
WO 03095441	20-11-2003	AU 2003224371 A1	11-11-2003

717
716

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 07-015793- -00000-0000
Fec: 2007-02-16 16:35:22 Dep: 2020 NUEVE CREACIONES
Tra: 11 PATENTES
Eve: 379 FASE NACIONAL
Act: 411 PRESENTACION Folios 716

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [x] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [x]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [x]
- Descripción de la invención [x]
- Dibujos de ser estos pertinentes [X]
- Comprobante de pago de las tasas establecidas [x]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

16 FEB. 2007

Fecha_____

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

717

Folio 718

2020
Bogotá D.C.,

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
PFIZER INC

REFERENCIA	Radicación No.	7 15793
	Solicitud internacional	PCT/IB2005/002697
	Fecha inicio fase nacional	18/03/2007
	Trámite	11
	Evento	379
	Actuación	416
	Oficio No.	2851
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 27 MAR 2007

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

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