Industria y Comercio

SUPERINTENDENCIA

06009548

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD P.C.T.

PATENTE DE INVENCIÓN

21 **EXPEDIENTE No.** 06009548

54 **TÍTULO** COMPUESTO DE BENZOXAZEPINA CON ACTIVIDAD INHIBIDORA DE ESCUALENO SINTASA Y REDUCTORA DE COLESTEROL Y TRIGLICERIDOS

51 **CLASIFICACIÓN INTERNACIONAL** C07D 267/14, 417/06, 413/06 A61K31/550, 31/427, 31/4245, 45/00, A61P43/00, 3/06, 3/00, 13/12, 9/10, 9/06

71 **SOLICITANTE** TAKEDA PHARMACEUTICAL COMPANY LIMITED

DOMICILIO OSAKA, JAPON

74 **APODERADO** EMILIO FERRERO
CC 938 019 de Usaquen

22 **BOGOTÁ, D. C.,**

(FORMA P 10)

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINDUSTRIA Y COMERCIO
Radicacion : 06009548 00000000 Folios: 737
Fecha (AMD): 2006-02-01 17:21:32
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

01-03-2006

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Radicacion : 06009548 00000000 Folios: 737
Fecha (AMD): 2006-02-01 17:21:32
Tramite : 011 PCT-PATENT 378 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☒ Capítulo I. ☐ Capítulo II

2 SOLICITANTE (71)

Nombre **TAKEDA PHARMACEUTICAL COMPANY LIMITED**
sociedad constituida y existente bajo las leyes de Japón

Dirección 1-1, Doshomachi 4-chome
Chuo-Ku, Osaka-shi
Osaka
Japón

Domicilio Osaka
Japón

IDENTIFICACIÓN

C C ☐ NIT ☐
C.E ☐ Otro ☐
Cual ____
Número ____

3 REPRESENTANTE O APODERADO

Nombre EMILIO FERRERO
Dirección Carrera 4ª No 72-35
Teléfono. 347 36 11
Fax 211 86 50
E-mail clientes@camyp com
Domicilio Bogotá, Colombia

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 438 019 T P 31.929

4 INVENTOR (ES) (72)

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Osaka
Japón

5 PCT (86)

Solicitud Internacional No PCT/JP2004/011293 Fecha: 30 de julio de 2004
Publicación Internacional No WO 2005/012272 A1 Fecha. 10 de febrero de 2005

6 Título (54)

COMPUESTO DE BENZOXAZEPINA

Ver Folio # 749

2

7 **Clasificación Internacional (51)** C07D 267/14, A01N 43/06, 43/06, A61K 31/553, 31/427 31/4245, 45/00, A61P 43/00, 3/06, 3/00, 13/12, 9/10, 9/06.

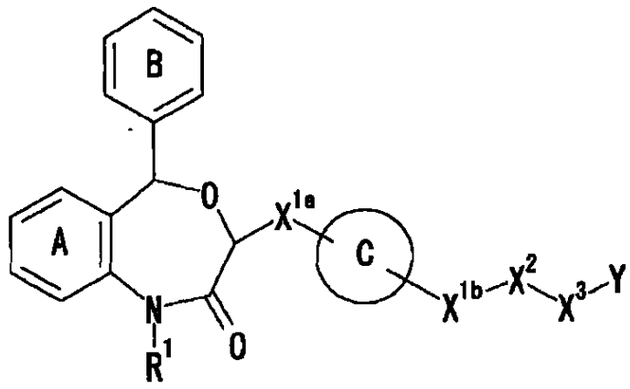
8 **Prioridad** SI☒ NO☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	JP	1 de agosto de 2003	2003-285341

9 **Comprobante de pago No.:** _____ **Fecha:** _____

10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 463 000 oo.
- ☐ Comprobante de pago por reivindicación de prioridad
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- ☒ Poderes, si fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar 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 12x12
- ☐ 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.
- ☒ Otros VER HOJA DE DOCUMENTOS ANEXOS

(11) **FIGURA CARACTERÍSTICA**



(12) Solicito la concesión de la patente,

NOMBRE EMILIO FERRERO

FIRMA :

C C. 438.019 de Usaquén T.P. 31.929

JDF

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2005/012272 **A1**
   Descripción.
   Páginas 346 en el idioma original
   Páginas 361 en español
   Reivindicaciones: Número (s) 33
2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.
3. ☒Forma PCT/IB306/ Notification of the recording of a change
4. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN FASE INTERNACIONAL

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, D - COLOMBIA

179

Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation and Power-of- Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER- OF- ATTORNEY

14656
08085

Yo (nosotros), abajo firmado (s)/I (we), the undersigned
TAKEDA PHARMACEUTICAL COMPANY LIMITED
domiciliado (s) en/of 1-1, Doshomachi 4-chome,
Chuo-ku, Osaka-shi, Osaka Japan

por el presente nombramos a EMILIO FERRERO, tpa 31929, GONZALO PERDOMO, tpa 831, LUZ CLEMENCIA DE PAEZ, tpa 23555 y GERMAN CAVELIER, tpa 832, domiciliados en la Carrera 4ª N° 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero, y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

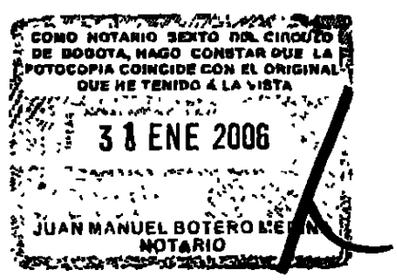
Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen, su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria, y el registro de licencias de uso de esos derechos. b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos, acciones y procesos que promovamos o se nos

in due compliance with the terms of paragraph 1st of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa 31929, GONZALO PERDOMO, tpa 831, LUZ CLEMENCIA DE PAEZ, tpa 23555 and GERMAN CAVELIER, tpa 832, domiciled at Carrera 4ª N° 72 35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad, and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs, the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin, its renewal, assignment, change of name or domicile, voluntary cancellation, and the registration of licenses of use of the above rights. b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative and Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights, actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit

DE BOGOTÁ PARA CONSTAR QUE LA FOTOCOPIA QUE ANTECEDE COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
13 ENE. 2006
MANUEL ROTERO HERNANDEZ
NOTARIO

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COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
31 ENE 2006
JUAN MANUEL BOTERO
NOTARIO

promuevan Y para que en todos los asuntos arriba determinados, puedan sustituir, este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos

the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney

Dado y firmado hoy/Given and signed this 14th day of December, 2004

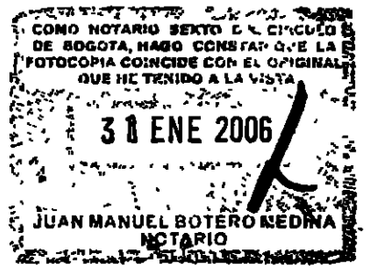
en/in Osaka, Japan

por/by

Firma Hiroshi Akimoto Ph. D. Signature
Executive Director
Member of the Board, General Manager,
Intellectual Property Dept.
Authorized Signing Officer

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
31 ENE 2006
JUAN MANUEL BOTERO MEDINA
NOTARIO

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WPPODE01-179 (MINUTA 12 1 1 2 5)


CONO NOTARIO SEXTO D L CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
31 ENE 2006
JUAN MANUEL BOTERO MEDINA
NOTARIO

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

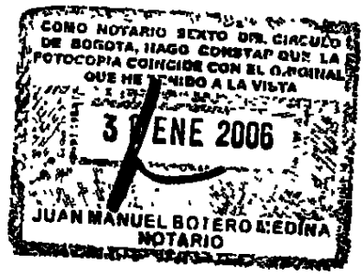
1. Country: **JAPAN**

   This public document

2. has been signed by — Kiyoomi FUJITA

3. acting in the capacity of — Notary Public of the Osaka Legal Affairs Bureau

4. bears the seal/stamp of — Kiyoomi FUJITA, Notary Public



Certified

5. at **Osaka** — 6. DEC. 17. 2004

7. by ***the Ministry of Foreign Affairs***

8. No. 04149

9. Seal/stamp:

10. Signature:

Tsutomu HIGUCHI

For the Minister for Foreign Affairs

大阪法務局所属　公証人役場

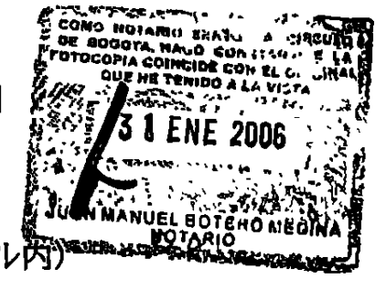
認証登簿　平成１６年第　334　号

嘱託人 武田薬品工業株式会社 常務取締役　知的財産部長 秋元浩

は、本職の面前でこの証書に署名した。

よって、その署名が本人の自筆であることを証する。

平成　16　年　12　月　14　日

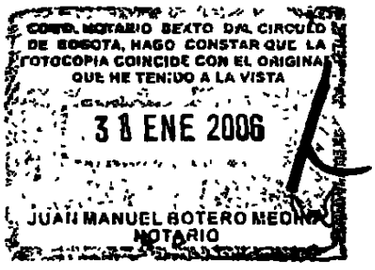


大阪市西区江戸堀１丁目１０番８号（帝人殖産ビル内）

公証人　**藤田清臣**　役場において

大阪法務局所属

公証人　藤田清臣


COPIA NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
31 ENE 2006
JUAN MANUEL BOTERO MEDINA
NOTARIO

REGISTER NUMBER 334 / 2004

I hereby certify that this document was signed before me and that the signature appearing on the same is the true signature of Hiroshi Akimoto, Ph. D., Executive Director, Member of the Board, General Manager, Intellectual Property Department of Takeda Pharmaceutical Company Limited.

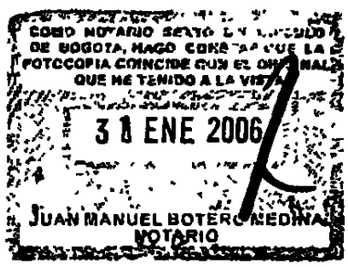
COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, DIGO CONSTA QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
30 ENE 2006
JUAN MANUEL GOTERO Y SILVA
NOTARIO

Dated this 14th day of December, 2004

10-8, Edobori 1-chome,
Nishi-ku, Osaka, Japan.

Kiyoomi Fujita

Kiyoomi Fujita
Notary attached
to The Osaka Legal
Affairs Bureau


DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
31 ENE 2006
JUAN MANUEL BOTERO MEDINA
NOTARIO

10

総第 3603 号

証　　明

大阪法務局所属公証人　**藤田清臣**

平成 16年12 月14 日付

平成16年 登簿 第 334 号

この認証の付与は，在職中の公証人がその権限に基づいてしたものであり，かつ，その押印は，真実のものであることを証明する。

COMO NOTARIO [illegible] DE BOGOTA, HAGO CONSTA[illegible] FOTOCOPIA COINCIDE CON EL ORIGINAL QUE [illegible] A LA VISTA

11 ENE 2006

JUAN MANUEL BOTERO [illegible]
NOTARIO

平成16年12月17日
平成　　年　　月　　日

大阪法務局長　**梅津和宏**

CERTIFICATE

This is to certify that the annexed Notarial Certificate has been executed by Notary,duly authorized and practising in Osaka, Japan, and that the Official seal appearing on the same is genuine.

Date 04.12.17

Director of the Osaka Legal Affairs Bureau

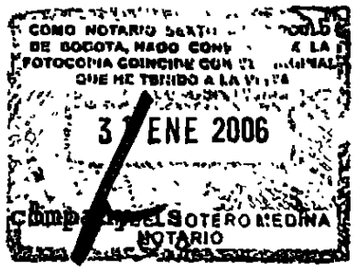
THE OSAKA CHAMBER OF COMMERCE & INDUSTRY

2-8 HOMMACHIBASHI, CHUO-KU, OSAKA 540-0029, JAPAN
FAX (06)6944-6248 TEL : (06)6944-~~6912~~ 6411
URL http //www osaka cci or jp/

November 17, 2004

To whom it may concern:

CERTIFICATE OF MEMBERSHIP



This is to certify that the undermentioned company is registered as a member of this Chamber.

Company name: Takeda Pharmaceutical Company Limited

(The former company name in English was Takeda Chemical Industries, Ltd. until June 29, 2004.)

Address: 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan

Membership Number: KT-01-00080

The Osaka Chamber of Commerce & Industry

Yoshinobu Kobayashi
Authorized Signatory

A №009149

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 FEB -4 A 2:33

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

38 ENE 2006

JUAN MANUEL DUCRO LEDINA
NOTARIO

EMBAJADA DE COLOMBIA - SECCION CONSULAR

Tokio, Japón, DICIEMBRE 20, 2004
No 299

El encargado de las funciones consulares de Colombia

CERTIFICA

Que el (la) Señor(a) YOSHINOBU KOBAYASHI, quien autoriza el presente documento , es la persona legalmente facultada para representar en la fecha señalada al (a la) CAMARA DE COMERCIO E INDUSTRIA, OSAKA y que la firma y sello que en el documento aparecen como suyos son las que usa y acostumbra para sus actos oficiales

El Encargado de Funciones Consulares no asume responsabilidad alguna por el contenido del documento

Firma del Encargado de Funciones Consulares

Derechos. US$23 oo

RAFAEL RICARDO OROZCO
Segundo Secretario

DE RELACIONES
ERIORES

085749

LA FIRMA APARECE EN EL
DOCUMENTO DE SEMPEÑA
LAS FUNCIONES INDICADAS

TRADUCCIÓN OFICIAL No. 02.04/05b realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia y registrado ante el Ministerio de Relaciones Exteriores de Colombia.

A continuación se traducen los sellos y legalizaciones de un documento por medio del cual **TAKEDA PHARMACEUTICAL COMPANY LIMIMTED** domiciliado en el 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka, Japón, otorga derechos de Representación y Poder a los Doctores EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PÁEZ, tpa. 23555; y GERMÁN CAVELIER, tpa. 832, domiciliados en la Carrera 4 No. 72-35, Bogotá, Colombia.

Dado y firmado el 14 de diciembre de 2004 en Osaka, Japón.

Firma Ilegible

Firma Hiroshi Akimoto Ph. D.
Director Ejecutivo
Miembro de la Junta, Gerente General,
Departamento de Propiedad Intelectual
Signatario Autorizado

NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
30 ENE 2006
JUAN MANUEL BOTERO MEDINA
NOTARIO

REGISTRO NÚMERO **334** / 2004

Por el presente certifico que este documento fue firmado ante mí y que la firma que aparece en el mismo es la firma auténtica de Hiroshi Akimoto, Ph. D., Director Ejecutivo, Miembro de la Junta, Gerente General, Departamento de Propiedad Intelectual de Takeda Pharmaceutical Company Limited.

Expedido hoy 14 de diciembre de 2004

10-8, Edobori 1-chome

Nishi-ku, Osaka, Japón

Firma ilegible

Kiyoomi Fujita
Notario adjunto a la
Oficina de Asuntos Legales de Osaka

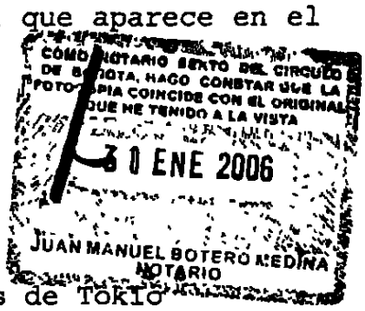
DOCUMENTO ANTERIOR EN JAPONÉS

(Anexo)

Texto en Japonés

CERTIFICADO

El presente es para certificar que el Certificado Notarial anexo ha sido suscrito por un notario debidamente autorizado y en ejercicio en Osaka, Japón, y que el sello oficial que aparece en el mismo es auténtico.



Fecha: 04.12.17

Director de la Oficina de Asuntos Legales de Tokio

APOSTILLA

(Convention de La Haye du 5 octubre 1961)

1. País: **JAPÓN**

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2. ha sido firmado por Kiyoomi FUJITA

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4. lleva el sello/estampilla de Kiyoomi FUJITA, Notario Público

Certificado

5. en **Osaka** 6. DIC 17 DE 2004

7. por el **Ministerio de Relaciones Exteriores**

8. **No. 04149**

DIEGO F. VARGAS
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLES – INGLES - ESPAÑOL
RES 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA

9. **Sello/estampilla** 10. **Firma:**

MINISTERIO DE RELACIONES EXTERIORES · JAPÓN ·

Firma Ilegible

Tsutomu HIGUCHI

Por el Ministro de Relaciones Exteriores

LA CÁMARA DE COMERCIO E INDUSTRIA DE OSAKA
2-8 HOMMACHIBASHI, CHUO-KU, OSAKA 540-0029, JAPÓN
FAX (06) 6944-6248 TEL 6944-~~5413~~ 6411
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Noviembre 17 de 2004

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DE COMERCIO SEXTO DEL CIRCUITO DE BOGOTÁ DC CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
31 ENE 2006
JUAN MANUEL BOTERO LEDINA NOTARIO

CERTIFICADO DE MEMBRESÍA

El presente es para certificar que la siguiente compañía está registrada como miembro de esta Cámara.

Nombre de la compañía: Takeda Pharmaceutical Company Limited

(El nombre anterior de la compañía en inglés fue Takeda Chemical Industries, Ltd. hasta el 29 de junio de 2004.)

Dirección: 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japón

Número de Membresía: KT-01-00080

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE
BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S) DE:

Diego Fernando

CORRESPONDE A LA FIRMA INSCRITA POR
EL (LOS) EN ESTA NOTARIA
SANTAFE DE BOGOTA, 08 FEB 2005

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

31 ENE 2006

JUAN MANUEL OTERO MEDINA
NOTARIO

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08 FEB -8 P 2:39

313391

JEFE DE LEGALIZACIONES
BOGOTA D.C.

FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

La Cámara de Comercio e Industria de Osaka

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Yoshinobu Kobayashi

Signatario Autorizado

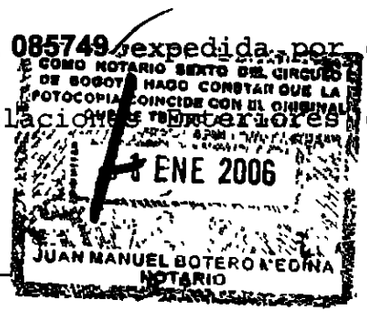
(Respaldo)

Certificado No. 299 del 20 de diciembre de 2004 expedido por la EMBAJADA DE COLOMBIA en Tokio, Japón, en donde se certifica que YOSHINOBU KOBAYASHI está legalmente facultado para firmar a nombre de la Cámara de Comercio e Industria de Osaka y que su firma en el anterior documento es auténtica.

Firmado por RAFAEL RICARDO OROZCO, Segundo Secretario.

Pagados los derechos consulares.

Legalización de la firma anterior con el **No. 085749** expedida por el Jefe de Legalizaciones del Ministerio de Relaciones Exteriores en Santafe de Bogotá el 4 de febrero de 2005.



Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

DVZ/ID-6472/WPCL002G/COLO 14656-845-001-0

DIEGO F. VARGAS Z.
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLES – INGLES - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
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BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S)
Diego Echeverri
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EL(ELLOS) EN ESTA NOTARIA
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REPUBLICA DE COLOMBIA
Notaría Sexta
SANTAFE DE BOGOTA D.C.

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BOGOTA D.C.

MINISTERIO DE
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313395

Diego Ucaga
CUALQUIER ENMENDADURA
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

COMO NOTARIO SEXTO DEL CIRCUITO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
30 ENE 2006
JUAN MANUEL BOTERO MEDINA
NOTARIO

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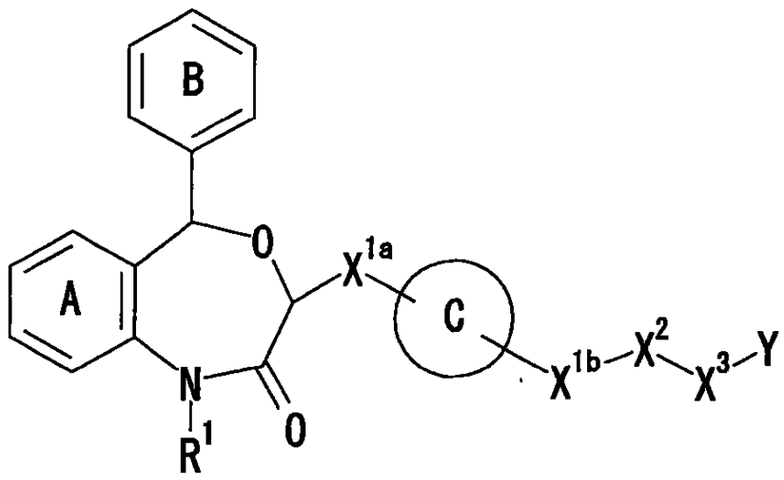
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(81) 指定国 (表示のない限り、全ての種類の国内保護が可能): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

[続葉有]

(54) Title: BENZOXAZEPINE COMPOUND

(54) 発明の名称: ベンズオキサゼピン系化合物



〔I〕

(57) Abstract: A compound represented by the formula [I] [I] (wherein ring A and ring B each represents an optionally substituted benzene ring, ring C represents an optionally further substituted aromatic ring, R^1 represents a lower alkyl optionally substituted by optionally substituted hydroxy, X^{1a} represents a bond or optionally substituted lower alkylene, X^{1b} represents a bond or optionally substituted lower alkylene, X^2 represents a bond, -O-, or -S-, X^3 represents a bond or an optionally substituted divalent hydrocarbon group, and Y represents optionally esterified or amidated carboxy) or a salt of the compound. The compound of the formula [I] is safer and has more potent lipid-lowering activity such as squalene synthase inhibitory activity (cholesterol-lowering activity) and triglyceride-lowering activity. The compound is useful as a medicine for, e g , the prevention of and treatments for hyperlipemia.

[続葉有]

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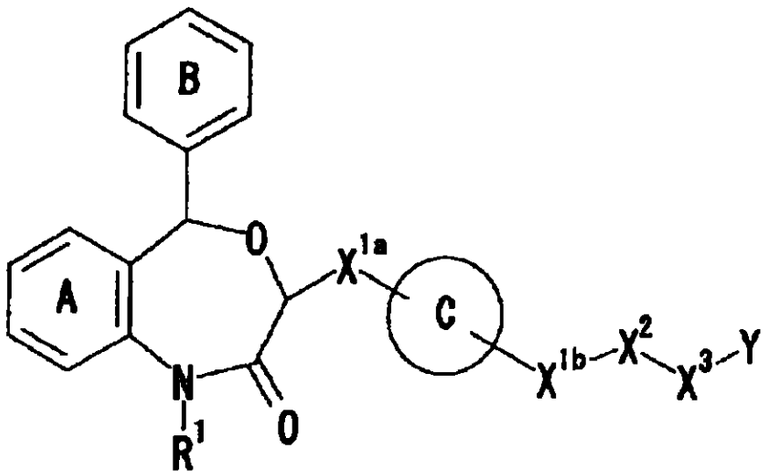
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(57) 要約:

式〔Ｉ〕



〔式中、環Ａおよび環Ｂはそれぞれ置換されていてもよいベンゼン環；環Ｃはさらに置換されていてもよい芳香環；R^1は置換されていてもよい水酸基で置換されていてもよい低級アルキル基；X^{1a}は結合手または置換されていてもよい低級アルキレン；X^{1b}は結合手または置換されていてもよい低級アルキレン；X^2は結合手、－Ｏ－または－Ｓ－；X^3は結合手または置換されていてもよい二価の炭化水素基；Ｙはエステル化またはアミド化されていてもよいカルボキシル基を示す。〕で表される化合物またはその塩。式〔Ｉ〕の化合物は、より安全で、かつ、より強力なスクアレン合成酵素阻害作用（コレステロール低下作用）、トリグリセライド低下作用等の脂質低下作用を有し、高脂血症の予防治療等の医薬として有用な化合物である。

BENZOXAZEPINE COMPOUND

Technical Field

The present invention relates to a novel benzoxazepine compound having squalene synthase inhibitory activity, cholesterol lowering activity and triglyceride lowering activity, which is useful for preventing or treating hyperlipemia and the like.

Background Art

Abnormal increase of the concentration of blood serum lipids is called hyperlipidemia or hyperlipemia. Blood serum lipids include cholesterol (cholesterol ester, free cholesterol), phospholipid (lecithin, sphingomyelin and the like), triglyceride (neutral lipid), free fatty acid, other sterols and the like, and specifically, the increase of cholesterol and triglyceride is a clinical issue (COMMON DISEASE SERIES No.19 hyperlipemia, Haruo Nakamura ed., published on October 10, 1991, by Nankodo).

Examples of a drug for lowering cholesterol level in blood include drugs that trap bile acid and inhibit its absorption such as Cholestyramine and Colestipol (for example, disclosed in U.S.P. 4,027,009) and drugs that inhibit acyl coenzyme A cholesterol acyltransferase (ACAT) and suppress intestinal absorption of cholesterol, such as

Melinamide. In addition, drugs that suppress cholesterol biosynthesis, such as Lovastatin (disclosed in U.S.P. 4,231,938), Simvastatin (disclosed in U.S.P. 4,444,784) and Pravastatin (disclosed in U.S.P. 4,346,227) which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, are used as medicaments.

Furthermore, as triglyceride lowering agents, fibric acid derivatives such as clofibrate (British Patent No. 860303), fenofibrate (German Patent No. 2250327) and the like are used as medicaments.

On the other hand, as compounds having inhibitory effect on biosynthesis of choresterol by inhibiting squalene synthase are disclosed in non-Patent Publications such as Journal of Medicinal Chemistry, 1988, vol.31, p.1869-1871; Expert Opinion on Therapeutic Patents, 1998, vol.8, p.521-530; Bioorganic Medicinal Chemistry, 2002, vol.10, p.385-400; Bioorganic Medicinal Chemistry, 2002, vol.10, p.401-412; Chemical & Pharmaceutical Bulletin, 2002, vol.50, p.53-58; Chemical & Pharmaceutical Bulletin, 2002, vol.50, p.59-65; Journal of Medicinal Chemistry, 2002, vol.45, p.4571-4580; and Patent Publications such as JP-A 1-213288, JP-A 2-101088, JP-A 2-235820, JP-A 2-235821, JP-A 3-20226, JP-A 3-68591, JP-A 3-148288, JP-A 9-087260, USP 5135935, USP 5726306, USP 5698691, EP 0645377, WO 92/15579, WO 93/09115, WO 95/021834, WO 97/10224, WO 2001/98282 and

USP 6537987.

Disclosure of Invention

It is very important to control the concentration of blood serum lipids properly for preventing or treating various diseases associated with arteriosclerosis including ischemic cardiac diseases and cerebral infarction. In addition, it is thought that hypertriglyceridemia induces pancreatic disorder. When HMG-CoA reductase is inhibited with a HMG-CoA reductase inhibitor, not only biosynthesis of cholesterol, but also biosynthesis of other components essential to living organism such as ubiquinone, dolichol and heme A are inhibited, resulting in side effects of concern. In addition, combination use of a triglyceride lowering agent and a statin compound is contraindicated due to hepatic toxicity. On the other hand, squalene synthase is an enzyme participating in an essential stage of the cholesterol biosynthesis pathway. This enzyme catalyzes reductive dimerization of two molecules of farnesyl pyrophosphate to form squalene.

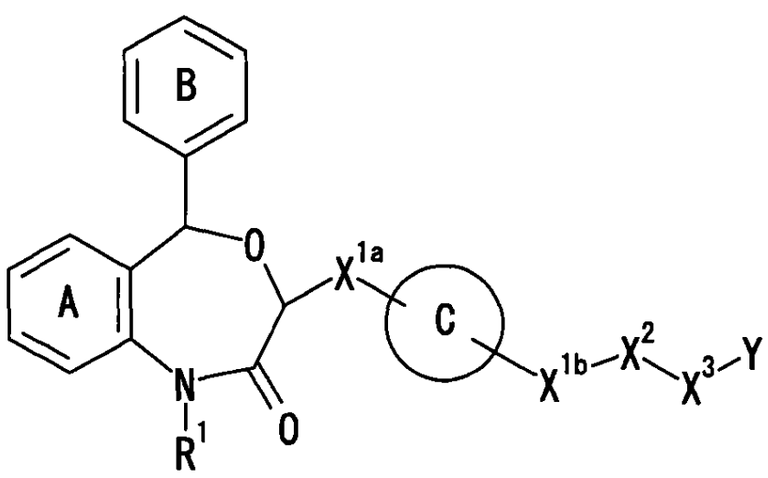
Under such circumstances, an object of the present invention is to provide a compound which is safer and has more potent lipid lowering activity such as squalene synthase inhibitory activity (cholesterol lowering activity) and triglyceride lowering activity, and thus is

useful as a drug for preventing or treating hyperlipemia.

The present inventors intensively studied and, as a result, for the first time, synthesized a 4,1-benzoxazepine compound characterized by a chemical structure having a particular substituent at the 3-position and found that this compound has unexpectedly excellent pharmaceutical effects such as lipid lowering effect based on its unique chemical structure, has high delivery in transference to a target organ and has a wide safety margin, which resulted in completion of the present invention.

That is, the present invention relates to:

(1) a compound represented by the formula [1]:



wherein ring A and ring B each represent an optionally substituted benzene ring, ring C represents an optionally further substituted aromatic ring, R^1 represents a lower alkyl group optionally substituted with an optionally substituted hydroxyl group, X^{1a} represents a bond or

optionally substituted lower alkylene, X^{1b} represents a bond or optionally substituted lower alkylene, X^2 represents a bond, -O- or -S-, X^3 represents a bond or an optionally substituted divalent hydrocarbon group, and Y represents an optionally esterified or amidated carboxyl group, or a salt thereof;

(2) the compound according to the above (1), wherein X^{1b} is a bond and Y is an optionally esterified carboxyl group;

(3) the compound according to the above (1), wherein ring A is a benzene ring substituted with halogen atom(s);

(4) the compound according to the above (1), wherein ring B is a benzene ring substituted with lower alkoxy group(s);

(5) the compound according to the above (1), wherein ring C is an optionally further substituted monocyclic aromatic heterocyclic ring;

(6) the compound according to the above (1), wherein ring C is an optionally further substituted benzene ring;

(7) the compound according to the above (1), wherein ring C is an optionally further substituted aromatic ring having no hydrogen atom that may be deprotonated;

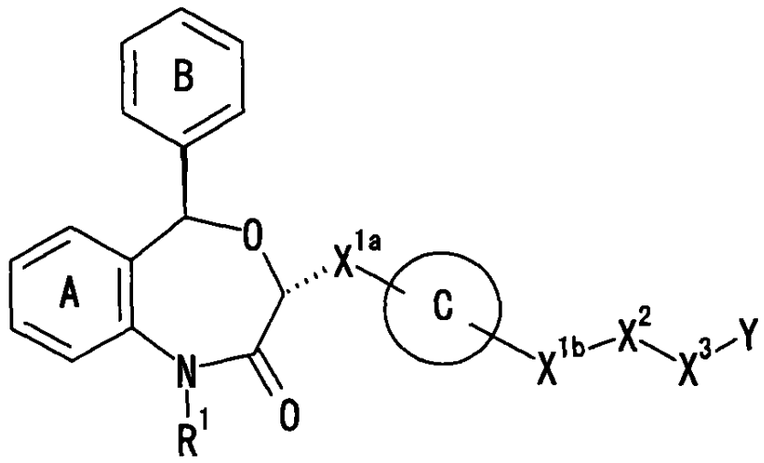
(8) the compound according to the above (1), wherein X^{1a} is C_{1-3} alkylene;

(9) the compound according to the above (1), wherein X^2 is a bond;

(10) the compound according to the above (1), wherein X^3 is

C_{1-4} alkylene;

(11) the compound according to the above (1), wherein the formula [I] is the formula [Ia]:



wherein respective symbols are as defined in the above (1);

(12) 3-(2-{3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]propyl}-1,3-thiazol-5-yl)propionic acid, 3-(2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1,3-thiazol-4-yl)propionic acid, or a salt thereof;

(13) (2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)propionic acid, (2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)acetic acid, or a salt thereof;

(14) 5-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic acid, 5-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic acid, 5-(3-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic acid, or a salt thereof;

(15) a prodrug of the compound according to the above (1);

(16) a medicine comprising the compound according to the above (1) or a prodrug thereof;

(17) a medicine comprising a combination of the compound according to the above (1) or a prodrug thereof and a cholesterol lowering agent;

(18) the medicine according to the above (16) or (17), which is a squalene synthase inhibitor;

(19) the medicine according to the above (16) or (17), which is a triglyceride lowering agent;

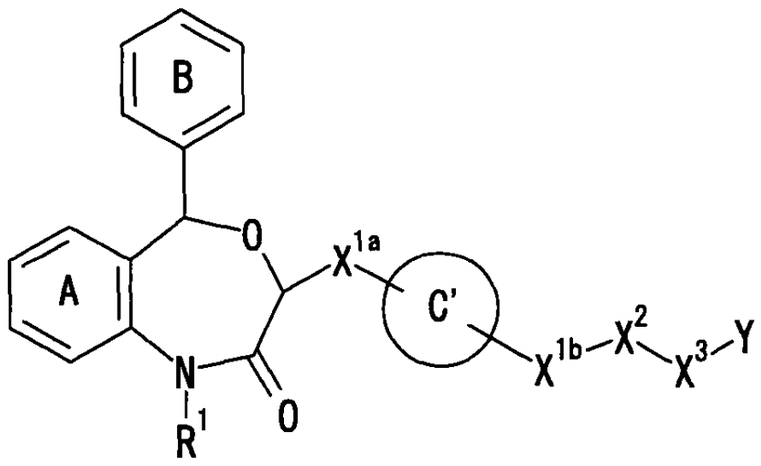
(20) the medicine according to the above (16) or (17), which is a lipid lowering agent;

(21) the medicine according to the above (16) or (17), which is an agent for preventing or treating hyperlipemia;

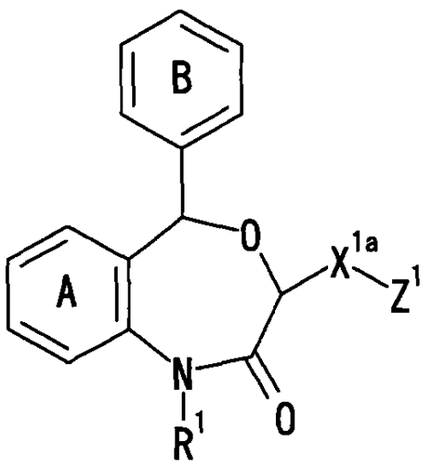
(22) the medicine according to the above (16) or (17),

which is a high density lipoprotein-cholesterol level elevating agent;

(23) a process for preparing a compound represented by the formula [I']:

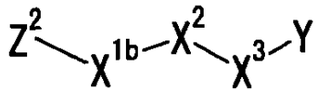


wherein ring C' represents an optionally further substituted aromatic heterocyclic ring and other symbols are as defined in the above (1), or a salt thereof, which comprises reacting a compound represented by the formula:



wherein Z^1 represents a functional group involved in an

aromatic heterocyclic ring forming reaction and other symbols are as defined in the above (1), or a salt thereof, with a compound represented by the formula:



wherein Z^2 represents a functional group involved in an aromatic heterocyclic ring forming reaction and other symbols are as defined in the above (1), or a salt thereof;

(24) a method of inhibiting squalene synthase in a mammal, which comprises administering an effective amount of the compound according to the above (1) or a prodrug thereof to said mammal;

(25) a method of lowering triglyceride level in a mammal, which comprises administering an effective amount of the compound according to the above (1) or a prodrug thereof to said mammal;

(26) a method of lowering lipid level in a mammal, which comprises administering an effective amount of the compound according to the above (1) or a prodrug thereof to said mammal;

(27) a method of preventing or treating hyperlipemia in a mammal, which comprises administering an effective amount of the compound according to the above (1) or a prodrug thereof to said mammal;

(28) a method of elevating high density lipoprotein-

cholesterol level in a mammal, which comprises administering an effective amount of the compound according to the above (1) or a prodrug thereof to said mammal;

(29) use of the compound according to the above (1) or a prodrug for manufacture of a squalene synthase inhibitor;

(30) use of the compound according to the above (1) or a prodrug thereof for manufacture of a triglyceride lowering agent;

(31) use of the compound according to the above (1) or a prodrug thereof for manufacture of a lipid lowering agent;

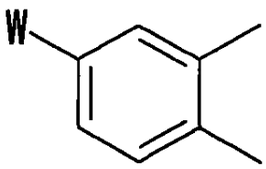
(32) use of the compound according to the above (1) or a prodrug thereof for manufacture of an agent for preventing or treating hyperlipemia;

(33) use of the compound according to the above (1) or a prodrug thereof for manufacture of a high density lipoprotein-cholesterol level elevating agent; and the like.

Detailed Explanation of the Invention

The substituent of the "optionally substituted benzene ring" represented by ring A includes halogen (e.g. fluorine, chlorine, bromine, iodine), an optionally substituted lower alkyl group having 1 to 4 carbon atoms (e.g. methyl, ethyl, propyl, butyl, tert-butyl etc.), an optionally substituted lower alkoxy group having 1 to 4 carbon atoms (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy etc.), a

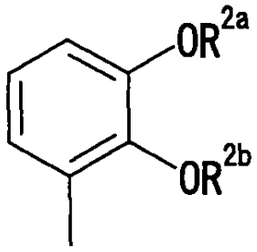
hydroxyl group, a nitro group and cyano. The ring A may have 1 to 3, preferably 1 to 2 of these substituents. The adjacent substituents of these substituents may be taken together to form a ring. The substituent of the optionally substituted lower alkyl group having 1 to 4 carbon atoms or the optionally substituted lower alkoxy group having 1 to 4 carbon atoms includes halogen (e.g. fluorine, chlorine, bromine, iodine), and 1 to 3 substituents may be at optional substitutable positions. The ring A is preferably a benzene ring substituted with halogen atoms, etc., more preferably a benzene ring substituted with a chlorine atom. The ring A is preferably a benzene ring represented by the formula:



wherein W represents a halogen atom (e.g. fluorine, chlorine, bromine, iodine) and inter alia, W is preferably a chlorine atom.

The substituent of the "optionally substituted benzene ring" represented by ring B includes the same number of the same groups as those exemplified above as the substituent of the "optionally substituted benzene ring" represented by ring A. The ring B is preferably a benzene ring substituted with a lower alkoxy group having 1 to 4 carbon

atoms, and inter alia, preferably a benzene ring represented by the formula:



wherein R^{2a} and R^{2b} represent independently a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms (e.g. methyl, ethyl, propyl, butyl etc.) and particularly preferably R^{2a} and R^{2b} are both methyl groups.

The aromatic ring of the "optionally further substituted aromatic ring" represented by ring C includes an aromatic hydrocarbon ring and an aromatic heterocyclic ring. The aromatic hydrocarbon ring includes, for example, a benzene ring, a naphthalene ring and the like, and preferred is a benzene ring. The aromatic heterocyclic ring (the aromatic heterocyclic ring of the "optionally further substituted aromatic heterocyclic ring" represented by ring C') includes, for example, an aromatic heterocyclic ring containing at least one (preferably 1 to 4, more preferably 1 to 2) of 1 to 3 kinds (preferably 1 or 2 kinds) of heteroatoms selected from an oxygen atom, a sulfur atom, a nitrogen atom and the like, as atoms constituting the ring system (ring atoms).

The aromatic heterocyclic ring includes 5- to 6-membered monocyclic aromatic heterocyclic rings such as furan, thiophene, pyrrole, oxazole, isoxazole, thiazole, isothiazole, imidazole, pyrazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, furazan, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine and the like; 8- to 12-membered fused aromatic heterocyclic rings such as benzofuran, isobenzofuran, benzo[b]thiophene, indole, isoindole, 1H-indazole, benzimidazole, benzoxazole, 1,2-benzisoxazole, benzothiazole, benzopyrane, 1,2-benzisothiazole, 1H-benzotriazole, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, naphthyridine, purine, pteridine, carbazole, α-carboline, β-carboline, γ-carboline, acridine, phenoxazine, phenothiazine, phenazine, phenoxathiine, thianthrene, phenanthridine, phenanthroline, indolizine, pyrrolo[1,2-b]pyridazine, pyrazolo[1,5-a]pyridine, imidazo[1,2-a]pyridine, imidazo[1,5-a]pyridine, imidazo[1,2-b]pyridazine, imidazo[1,2-a]pyrimidine, 1,2,4-triazolo[4,3-a]pyridine, 1,2,4-triazolo[4,3-b]pyridazine and the like (preferably a heterocyclic ring in which the aforementioned 5- to 6-membered monocyclic aromatic heterocyclic ring is fused with a benzene ring, or a heterocyclic ring in which the same or different two of the

aforementioned 5- to 6-membered monocyclic aromatic heterocyclic rings are fused, more preferably a heterocyclic ring in which the aforementioned 5- to 6-membered monocyclic aromatic heterocyclic ring is fused with a benzene ring) and the like.

The ring C is preferably a monocyclic aromatic heterocyclic ring, a benzene ring or the like, and inter alia, preferred is a 5-membered monocyclic aromatic heterocyclic ring such as pyrazole, imidazole, thiazole, oxazole, isoxazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole or the like.

Although the ring C may be an aromatic ring having a hydrogen atom that may be deprotonated or an aromatic ring having no hydrogen atom that may be deprotonated, an aromatic ring having no hydrogen atom that may be deprotonated is preferred. The aromatic ring having no hydrogen atom that may be deprotonated includes, in addition to an aromatic ring originally having no hydrogen atom that may be deprotonated (e.g. benzene ring, thiazole, oxazole, isoxazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole etc.), an aromatic ring in which a hydrogen atom that may be deprotonated is substituted (e.g. pyrrole, pyrazole, imidazole etc. whose hydrogen atom on the ring-constituting nitrogen atom is substituted or which is bound to X^{1a} or/and X^{1b} via the ring-constituting nitrogen atom).

The substituent, which the aromatic ring of the "optionally further substituted aromatic ring" represented by ring C may have, includes (i) a carboxyl group optionally esterified with an optionally halogenated C_{1-6} alkyl group or an optionally halogenated C_{6-10} aryl-C_{1-4} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, phenyl, benzyl etc.), (ii) a phosphoric acid group optionally mono- or di-substituted with optionally halogenated C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, isopentyl, neopentyl, hexyl etc.) or C_{2-7} alkanoyloxy-C_{1-6} alkyl such as acetoxymethyl or pivaloyloxymethyl, (iii) a sulfonic acid group, (iv) a sulfonamide group optionally substituted with an optionally halogenated C_{1-6} alkyl group or an optionally halogenated C_{6-10} aryl-C_{1-4} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, benzyl etc.), (v) a hydroxyl group and a sulfhydryl group, which may be optionally substituted with an optionally halogenated C_{1-3} alkyl group (e.g. methyl, ethyl, propyl etc.), (vi) a carbamoyl group, (vii) a phenyl group optionally substituted with 1 to 5 substituents [e.g. hydroxyl group, chlorine, fluorine, aminosulfonyl group, amino group optionally substituted with C_{1-3} alkyl group (e.g. methyl, ethyl, propyl etc.)] and optionally bound to the aromatic ring via O or S, (viii) an amino group optionally mono- or

di-substituted with an optionally halogenated C_{1-3} alkyl group (e.g. methyl, ethyl, propyl etc.), (ix) a cyclic amino group optionally substituted with 1 to 3 C_{1-3} alkyl (e.g. methyl, ethyl etc.), benzyl, phenyl and the like (e.g. a 5- to 6-membered cyclic amino group optionally containing an oxygen atom or a sulfur atom in addition to nitrogen atoms as ring-constituting atoms, such as a cyclic amino group derived (by removing one hydrogen atom) from cyclic amine such as piperidine, pyrrolidine, morpholine, thiomorpholine, piperazine, 4-methylpiperazine, 4-benzylpiperazine, 4-phenylpiperazine, 1,2,3,4-tetrahydroisoquinoline or phthalimide), (x) a 5- to 6-membered aromatic heterocyclic group containing 1 to 4 heteroatoms selected from N, O and S and optionally bound to the aromatic ring via O or S (e.g. pyridyl, imidazolyl, indolyl, tetrazolyl etc.), (xi) a halogen atom (e.g. chlorine, fluorine, bromine, iodine etc.), (xii) a C_{1-4} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl etc.), a C_{1-4} alkoxy group (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy etc.) or a C_{1-4} alkylthio group (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio, tert-butylthio etc.), each of which may be optionally substituted with a substituent selected from a halogen atom, a C_{1-4} alkoxy group, a C_{1-4} alkylthio group, carboxyl and phenyl, (xiii) a C_{5-7}

cycloalkyl group (e.g. cyclopentyl, cyclohexyl, cycloheptyl etc.), and (xiv) optionally halogenated C_{1-7} alkanoyloxy (e.g. formyloxy, acetoxy, propionyloxy, butyryloxy, tert-butoxycarbonyloxy, isobutyryloxy, valeryloxy, pivaloyloxy etc.). The "optionally further substituted aromatic ring" may be substituted with 1 to 6, preferably 1 to 3 such substituents at substitutable positions. Two of such substituents may be taken together to form C_{3-6} alkylene, C_{3-6} alkyleneoxy, C_{3-6} alkylenedioxy or the like. For example, when two adjacent substituents on a phenyl group are linked each other to form C_4 alkylene, a tetrahydronaphthyl group is formed.

The lower alkyl group of the "lower alkyl group optionally substituted with an optionally substituted hydroxyl group" represented by R^1 includes, for example, C_{1-6} alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, isopentyl, neopentyl, hexyl and the like. Among them, a C_{3-6} alkyl group is preferred and a C_{4-5} alkyl group is more preferred. Inter alia, a branched C_{4-5} alkyl group such as isobutyl, neopentyl or the like is preferred.

The substituent, which the lower alkyl group of the "lower alkyl group optionally substituted with an optionally substituted hydroxyl group" represented by R^1 may have, includes a hydroxyl group optionally substituted

with C_{2-20} alkanoyl or C_{1-7} alkyl. Such substituent includes, for example, a hydroxyl group, acetyloxy (acetoxy), propionyloxy, tert-butoxycarbonyloxy, palmitoyloxy, dimethylaminoacetyloxy, 2-aminopropionyloxy and the like. The lower alkyl group may be substituted with 1-3 such substituents at substitutable positions.

Examples of R^1 include 1-propyl, 1-isopropyl, 1-isobutyl, 1-neopentyl, 2,2-dimethyl-3-hydroxypropyl, 3-hydroxy-2-hydroxymethyl-2-methylpropyl, 3-acetoxy-2,2-dimethylpropyl, 3-acetoxy-2-hydroxymethyl-2-methyl-propyl, 3-acetoxy-2-acetoxymethyl-2-methylpropyl, [1-(hydroxymethyl)cyclobutyl]methyl and the like. Among them, preferred are 2,2-dimethyl-3-hydroxypropyl, 3-hydroxy-2-hydroxymethyl-2-methylpropyl, 3-acetoxy-2,2-dimethylpropyl, 3-acetoxy-2-hydroxymethyl-2-methylpropyl, 3-acetoxy-2-acetoxymethyl-2-methylpropyl and the like.

The lower alkylene of the "optionally substituted lower alkylene" represented by X^{1a} includes, for example, C_{1-6} alkylene such as methylene, dimethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and the like. Among them, preferred is straight chain C_{1-4} alkylene such as methylene, dimethylene, trimethylene, tetramethylene or the like, and more preferred is straight chain C_{1-3} alkylene.

The substituent, which the lower alkylene of the "optionally substituted lower alkylene" represented by X^{1a}

may have, includes the same groups as those exemplified above as the substituent, which the aromatic ring of the "optionally further substituted aromatic ring" represented by ring C may have, an oxo group and the like. The "lower alkylene" may be substituted with 1 to 6, preferably 1 to 3 such substituents at substitutable positions.

X^{1a} is preferably a bond or straight chain C_{1-3} alkylene, and particularly preferably methylene.

The lower alkylene of the "optionally substituted lower alkylene" represented by X^{1b} includes the same groups as those exemplified as the lower alkylene of the "optionally substituted lower alkylene" represented by X^{1a}. The substituent, which the lower alkylene of the "optionally substituted lower alkylene" represented by X^{1b} may have, includes the same number of the same groups as those exemplified as the substituent which the lower alkylene of the "optionally substituted lower alkylene" represented by X^{1a} may have.

X^{1b} is preferably a bond or straight chain C_{1-3} alkylene, and particularly preferably a bond.

X^2 is preferably a bond.

The "divalent hydrocarbon group" of the "optionally substituted divalent hydrocarbon group" represented by X^3 includes a group formed by removing one hydrogen atom from a hydrocarbon group. The hydrocarbon group includes a C_{1-7}

straight or branched chain alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 1,1-dimethylethyl, n-pentyl, 3-methylbutyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, n-hexyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 2-ethylbutyl, 1-ethylbutyl, neopentyl, hexyl, heptyl), a C_{3-7} cycloalkyl group (cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexylmethyl etc.), a straight or branched chain C_{2-6} alkenyl group (e.g. vinyl, allyl, isopropenyl, 2-methylallyl, 1-propenyl, 2-methyl-1-propenyl, 2-methyl-2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl etc.), a C_{6-10} aryl group (e.g. phenyl, naphthyl), a C_{7-14} arylalkyl group (e.g. benzyl, phenethyl, naphthylmethyl) and the like.

The substituent, which the "divalent hydrocarbon group" of the "optionally substituted divalent hydrocarbon group" represented by X^3 may have, includes the same group as those exemplified above as the substituent which the lower alkylene of the "optionally substituted lower alkylene" represented by X^{1a} may have, optionally halogenated C_{1-6} alkylidene (e.g. methylidene, ethylidene, propylidene, isopropylidene, butenylidene etc.), vinylidene, cyclohexylidene, benzylidene and the like. The "divalent

hydrocarbon group" may be substituted with 1 to 6, preferably 1 to 3 such substituents at substitutable positions.

The "divalent hydrocarbon group" of the "optionally substituted divalent hydrocarbon group" represented by X^3 preferably includes (1) straight or branched chain alkylene in which the number of carbon atoms constituting the straight chain part is 1 to 7 (preferably 1 to 4) (e.g. methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, propylene, ethylmethylene, ethylethylene, propylethylene, butylethylene, methyltetramethylene, methyltrimethylene etc.), (2) a double bond- containing carbon chain in which the number of carbon atoms constituting the straight chain part is 2 to 7 (preferably 2 to 4) (e.g. vinylene, propenylene, butenylene, butadienylene, methylpropenylene, ethylpropenylene, propylpropenylene, methylbutenylene, ethylbutenylene, propylbutenylene, methylbutadienylene, ethylbutadienylene, propylbutadienylene, pentenylene, hexenylene, heptenylene, pentadienylene, hexadienylene, heptadienylene etc.), (3) phenylene (e.g. 1,2-phenylene, 1,3-phenylene, 1,4-phenylene etc.) and (4) a divalent group in which phenylene and alkylene and/or alkenylene are combined (e.g. $-CH_2-C_6H_4-$, $-CH_2CH_2-C_6H_4-$, $-CH_2-C_6H_4-CH_2-$ etc.).

X^3 is preferably C_{1-4} alkylene such as methylene,

ethylene, trimethylene, tetramethylene or the like, vinylene, propenylene, phenylene or the like.

The "optionally esterified or amidated carboxyl group" represented by Y includes carboxyl, lower alkoxycarbonyl having 2 to 7 carbon atoms (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, sec-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl etc.), C_{7-14} aryloxycarbonyl (e.g. phenoxycarbonyl, 1-naphthoxycarbonyl), C_{8-12} aralkyloxycarbonyl (e.g. benzyloxycarbonyl etc.), carbamoyl, N-C_{1-6} alkylcarbamoyl, N,N-diC_{1-6} alkylcarbamoyl, N-C_{8-12} aralkylcarbamoyl, N,N-diC_{8-12} aralkylcarbamoyl, 1-pyrrolidinylcarbonyl, piperidinocarbonyl, morpholinocarbonyl and the like. Among them, Y is preferably carboxyl, methoxycarbonyl, ethoxycarbonyl or the like, and particularly preferably carboxyl.

The compound represented by the formula [1] includes, particularly preferably, 3-(2-{3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]propyl}-1,3-thiazol-5-yl)propionic acid, 3-(2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1,3-thiazol-4-yl)propionic acid, (2-{[(3R,5S)-7-chloro-5-(2,3-

dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)propionic acid, (2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)acetic acid, 5-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic acid, 5-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic acid, 5-(3-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxodiazol-5-yl)pentanoic acid and the like.

The compound represented by the formula [I] may be in a free form or a pharmacologically acceptable salt form, and both forms are included in the scope of the present invention. When the compound represented by the formula [I] has an acidic group such as a carboxyl group, etc., the compound may form a salt with inorganic bases (e.g. alkali metal such as sodium, potassium etc., alkaline earth metal such as calcium, magnesium etc., transition metal such as zinc, iron, copper etc.) or organic bases (e.g. organic amines such as trimethylamine, triethylamine, pyridine,

picoline, ethanolamine, diethanolamine, triethanolamine, tris(hydroxymethyl)methylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and t-butylamine, basic amino acids such as arginine, lysine ornithine, and the like).

When the compound represented by the formula [I] of the present invention has a basic group such as an amino group or the like, the compound may form a salt with inorganic acids or organic acids (e.g. hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, carbonic acid, bicarbonic acid, formic acid, acetic acid, propionic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.) or acidic amino acids such as aspartic acid or glutamic acid.

The compound represented by the formula [I] or a salt thereof has asymmetric carbon atoms at the 3-position and the 5-position, and may be a mixture of stereoisomers. The isomers may be separated by a known means. Preferred is the trans form in which the substituents at the 3-position and 5-position are directed to the opposite direction each other relative to the plane of the 7-membered ring, and specifically preferred is a compound having the absolute configuration represented by the formula [Ia]. In addition,

the compound represented by the formula [I] or a salt thereof may be a racemic form or an optically active form, and the optically active form can be separated from the racemic form by a known optical resolution means.

A prodrug of the compound represented by the formula [I] or a salt thereof refers to a compound which is converted into the compound represented by the formula [I] or a salt thereof by a reaction with an enzyme or gastric acid under the physiological condition in vivo, that is, a compound which is changed into the compound represented by the formula [I] or a salt thereof by enzymatic oxidation, reduction, hydrolysis or the like, or a compound which is changed into the compound represented by the formula [I] or a salt thereof by hydrolysis with gastric acid or the like. The prodrug of the compound represented by the formula [I] or a salt thereof includes, when the compound represented by the formula [I] or a salt thereof has an amino group, a compound whose amino group is acylated, alkylated or phosphorylated (e.g. the compound represented by the formula [I] or a salt thereof whose amino group is eicosanoylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated or tert-butylated, etc.); when the compound represented by the formula [I] or a salt thereof

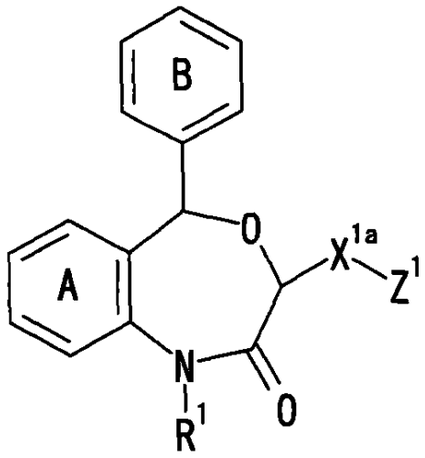
has a hydroxyl group, a compound whose hydroxyl group is acylated, alkylated, phosphorylated or borated (e.g. a compound whose hydroxyl group is acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, alanylated or dimethylaminomethylcarbonylated, etc.); and when the compound represented by the formula [I] or a salt thereof has a carboxyl group, a compound whose carboxyl group is esterified or amidated (e.g. a compound whose carboxyl group is ethylesterified, phenylesterified, carboxymethylesterified, dimethylaminomethylesterified, pivaloyloxymethylesterified, ethoxycarbonyloxyethylesterified, phthalidylesterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methylesterified, cyclohexyloxycarbonylethylesterified or methylamidated, etc.). These prodrugs can be prepared from the compound represented by the formula [I] or a salt thereof by a method known per se.

A prodrug of the compound represented by the formula [I] or a salt thereof may be a compound that is changed into the compound represented by the formula [I] or a salt thereof under the physiological condition as described in Development of Pharmaceutical Products, vol. 7, Molecular Design, 163-198, Hirokawa Shoten (1990).

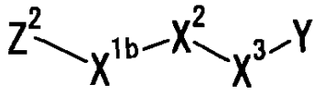
The compound represented by the formula [I] or a salt thereof may be hydrous or anhydrous.

The compound represented by the formula [I] or a salt thereof may be labeled with an isotope (e.g. ^{3}H, ^{14}C, ^{35}S, ^{125}I etc.).

The compound represented by the formula [I] or a salt thereof can be prepared, for example, by reacting a compound represented by the formula [II]:



wherein symbols are as defined above, or a derivative thereof with a compound represented by the formula:



wherein symbols are as defined above, or a salt thereof according to a method known per se (e.g. "Comprehensive Heterocyclic Chemistry", ed. by A.R.Katritzky and C.W.Rees, vol.4-6, Pergamon Press, Oxford, 1984), or thereafter forming an aromatic heterocyclic ring by cyclization reaction.

A combination of the "functional group involved in an

aromatic heterocyclic ring forming reaction" represented by Z^1 and Z^2 includes, for example:

(1) one is a carboxyl group and the other is 2-aminoalkanoyl group,

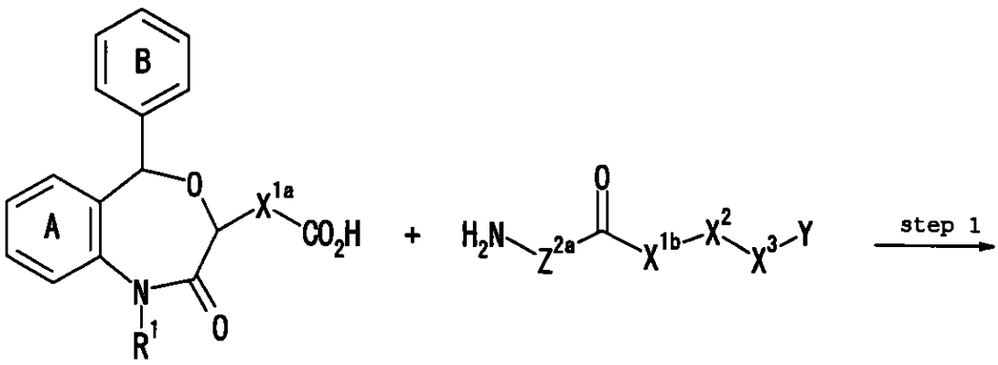
(2) one is a carboxyl group and the other is hydrazide,

(3) one is a thiocarbamoyl group and the other is an alkanoyl group substituted with a halogen atom at the 2-position, and

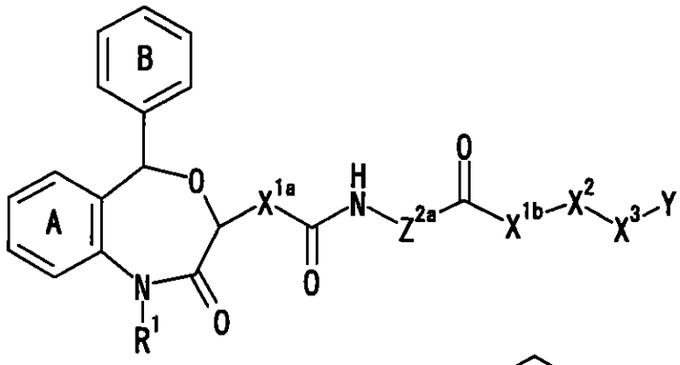
(4) one is a N-hydroxyamidino group and the other is carboxylic acid halide, or the like.

A method of preparing the compound represented by the formula [I'] includes Process A, Process B and the like, wherein a compound represented by the formula [II'] or a derivative thereof is used as the starting material.

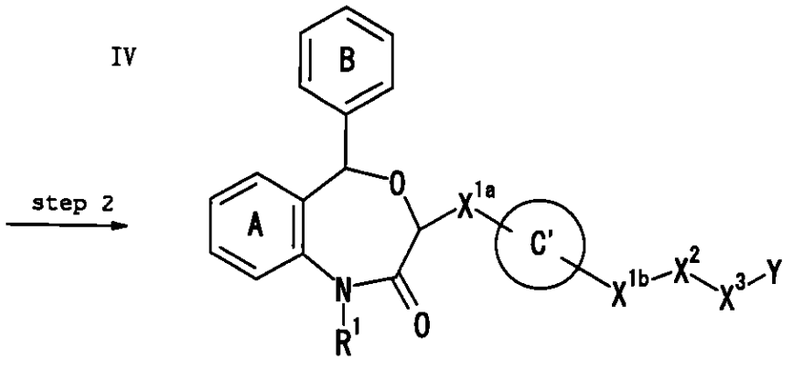
Process A



II'　　III

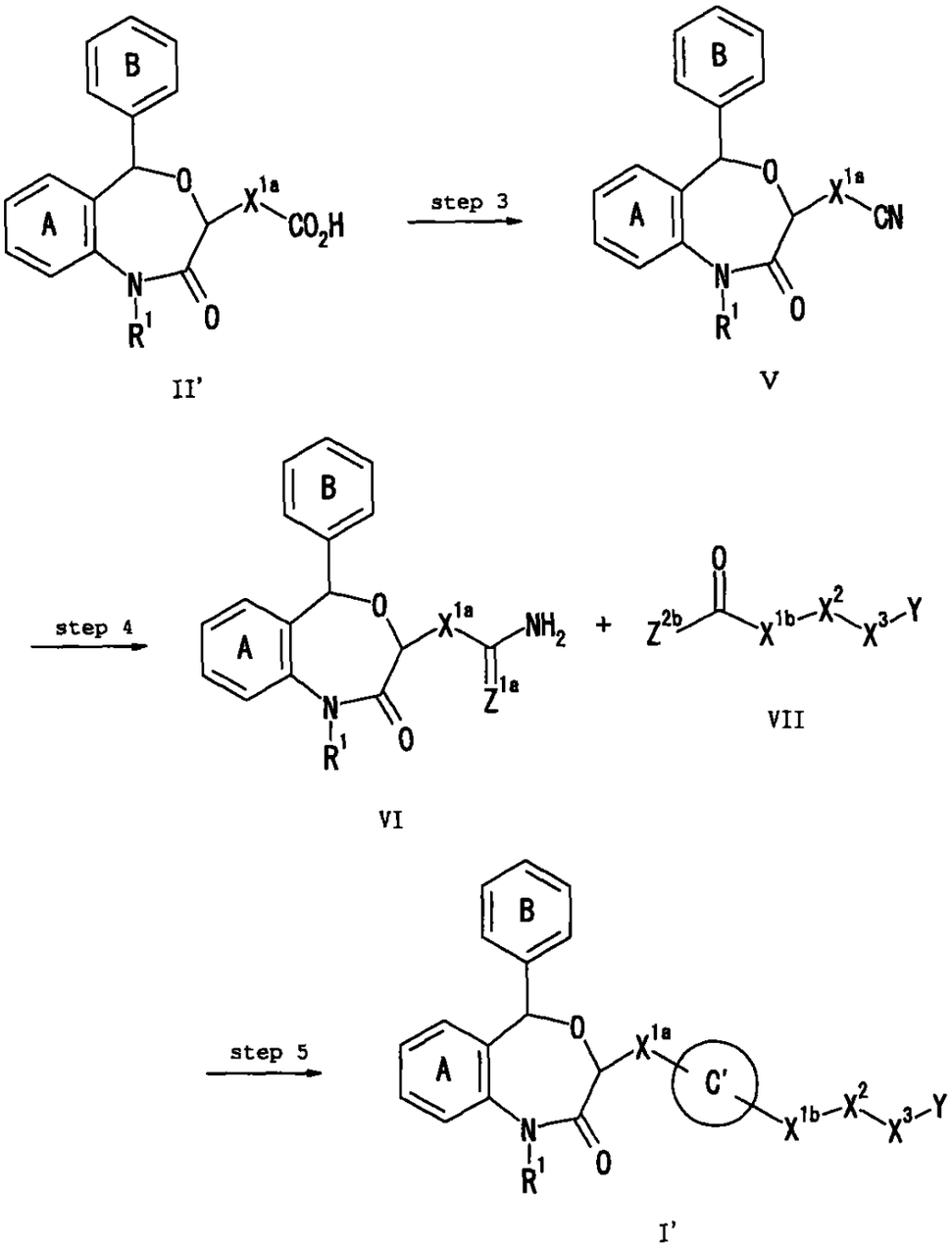


IV



I'

Process B



wherein, Z^{1a} represents a hydroxyimino group or a sulfur atom, Z^{2a} represents a methylene group or an imino group,

and Z^{2b} represents a halogen atom, or a lower alkyl group in which the carbon atom adjacent to the carbonyl group is substituted with one halogen atom.

In the step 1, a method of preparing the compound represented by the formula [IV] from the compound represented by the formula [II'] or a derivative thereof and the compound represented by the formula [III] includes, for example, a method comprising condensing the compound represented by the formula [II'] and the compound represented by the formula [III] with a generally known dehydration condensing agent in the presence of both compounds simultaneously, a method comprising activating the carboxylic acid of the compound represented by the formula [II'] by a generally known activating method and then reacting it with the compound represented by the formula [III], and a method comprising reacting a derivative of the compound represented by the formula [II'] with the compound represented by the formula [III].

The dehydration condensing agent includes, for example, N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, carbonyldiimidazole, 1H-benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate and the like.

A method of activating carboxylic acid includes, for example, a method comprising converting carboxylic acid

into acid anhydride with chloroformate, pivaloyl chloride or the like, a method comprising converting carboxylic acid into acid chloride with oxalyl chloride, thionyl chloride or the like, method comprising esterifying carboxylic acid with 1-hydroxybenzotriazole using a dehydration condensing agent or the like, and the like.

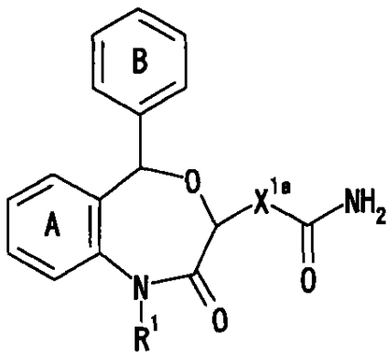
A method of reacting a derivative of the compound represented by the formula [II'] with the compound represented by the formula [III] includes a method comprising heating an ester derivative of the compound represented by the formula [II'] in the presence of the compound represented by the formula [III].

The compound represented by the formula [III] can be prepared, for example, according to Convenient Syntheses of δ-Aminolevulinic Acid, Ayelet Nudelman and Abraham Nodelman, Synthesis 1999, No. 4, pp568-570.

In the step 2, a method of preparing the compound represented by the formula [I] from the compound represented by the formula [IV] includes a method comprising treatment with Lawesson's reagent or phosphorus oxychloride ($POCl_3$).

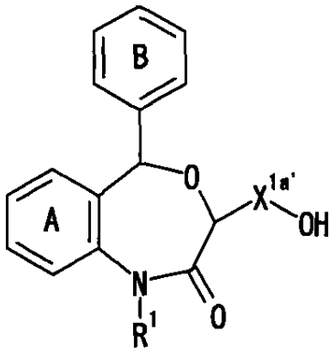
In the step 3, a method of preparing the compound represented by the formula [V] from the compound represented by the formula [II'] or a derivative thereof includes, for example:

1) a method of preparing the compound represented by the formula [V] using, as an intermediate, a compound represented by the formula [VIII]:



obtained from the compound represented by the formula [II'] by a generally known amidation method;

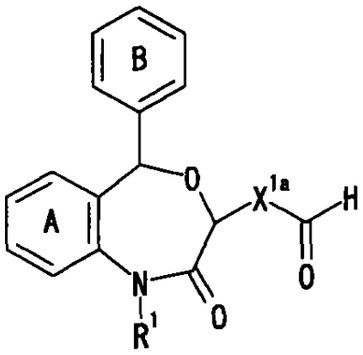
2) a method of preparing the compound represented by the formula [V] using, as an intermediate, a compound represented by the formula [IX]:



wherein $X^{1a'}$ represents an optionally substituted lower alkylene, obtained by a reduction reaction of carboxylic acid or a derivative thereof from the compound represented by the formula [II'] or a derivative thereof;

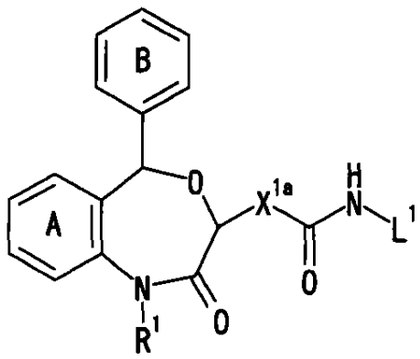
3) a method of preparing the compound represented by

the formula [V] using, as an intermediate, a compound represented by the formula [X]:



obtained by a generally known reduction reaction of carboxylic acid or a derivative thereof from the compound represented by the formula [II'] or a derivative thereof, or by a generally known oxidation reaction of alcohol from the compound represented by the formula [IX];
or the like.

An amidation method includes a method comprising condensation with ammonia or 1-hydroxybenzotriazole ammonia ($HOBt \cdot NH_3$) using a dehydration condensing agent and a method comprising preparation of amide represented by the formula [XI]:



wherein L^1 represents a protecting group for an amino group, followed by removal of the protecting group for an amino group.

A reduction reaction of carboxylic acid or a derivative thereof includes a reduction reaction of carboxylic acid or a derivative of carboxylic acid using a reducing agent such as lithium aluminum hydride, diisobutylaluminum hydride sodium borohydride, or the like.

An oxidation reaction of alcohol includes, for example, a method comprising treatment with a sulfur trioxide pyridine complex or oxalyl chloride in dimethyl sulfide, an oxidation method using an oxidizing agent such as pyridinium chlorochromate or Dess-martin reagent, etc. and the like.

A method of preparing the compound represented by the formula [V] from the compound represented by the formula [VIII] includes, for example, a method comprising treatment with anhydride such as trifluoromethanesulfonic acid anhydride, a method comprising treatment with a dehydration condensing agent such as carbonyldiimidazole in the presence of allyl bromide and the like.

A method of preparing the compound represented by the formula [V] from the compound represented by the formula [IX] includes, for example, a method comprising convertion of the hydroxyl group into a substitutable group followed

by treatment with cyanide, a method comprising Mitsunobu reaction in the presence of cyanide such as acetone cyanohydrin (a method comprising treatment with an azodicarboxylic acid derivative such as 1,1'-(azodicarbonyl)dipiperidine and an organic phosphorus compound such as tri-n-butylphosphine or triphenylphosphine) and the like.

A method of preparing the compound represented by the formula [V] from the compound represented by the formula [X] includes, for example, a method comprising reaction with an oxidizing agent such as iodine in aqueous ammonia, a method comprising Wittig reaction with phosphoric acid ester containing a cyano group in its molecule such as cyanomethylphosphoric acid diethylester followed by hydrogenation reaction and the like.

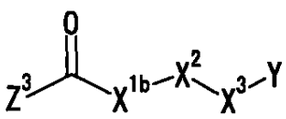
In the step 4, a method of preparing the compound represented by the formula [VI] from the compound represented by the formula [V] includes, for example, a method comprising treatment of the compound represented by the formula [V] with dithiophosphoric acid diethylester or the like, a method comprising treatment with hydroxylammonium chloride in the presence of an alkali such as sodium hydrogen carbonate.

In addition, a method of preparing the compound represented by the formula [VI] includes, for example, a

method comprising treatment of the compound represented by the formula [VIII] with a sulfurizing agent such as diphosphorus pentasulfide and the like.

In the step 5, a method of preparing the compound represented by the formula [I] from the compound represented by the formula [VI] and the compound represented by the formula [VII] includes, for example, a method comprising heating the compound represented by the formula [VI] in the presence of the compound represented by the formula [VII] and the like.

Among the compounds represented by the formula [VII], a compound represented by the formula [XII]:



wherein Z^3 represents a lower alkyl group in which it is substituted with a halogen atom on the carbon atom adjacent to the carbonyl group, may be prepared by, for example, Process C or the like.

Process C



XIII XII

wherein Z^4 represents a halogen atom.

In the step 6, a method of preparing the compound represented by the formula [XII] from the compound represented by the formula [XIII] includes, for example, a method comprising a reaction with diazomethane or trimethylsilyldiazomethane in a solution of hydrobromic acid in acetic acid and the like.

In each reaction of the process for preparing the compound [I] or a salt thereof and each reaction for synthesis of the starting compounds described above, when the starting compound has an amino group, a carboxyl group or a hydroxy group as a substituent, such a substituent may be protected with a protecting group which is usually used in peptide chemistry or the like. After reaction, if necessary, the protecting group can be removed to obtain the desired compound.

A protecting group for an amino group includes, for example, formyl, C_{1-6} alkylcarbonyl (e.g. acetyl, ethylcarbonyl etc.), phenylcarbonyl, C_{1-6} alkyl-oxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl etc.), phenyloxycarbonyl, C_{7-10} aralkyl-carbonyl (e.g. benzylcarbonyl etc.), trityl, phthaloyl, N,N-dimethylaminomethylene and the like, each of which may be optionally substituted. As such a substituent, a halogen atom (e.g. fluorine, chlorine, bromine, iodine etc.), C_{1-6} alkyl-carbonyl (e.g. methylcarbonyl, ethylcarbonyl,

butylcarbonyl etc.), a nitro group or the like is used and the number of substituents is about 1 to 3.

A protecting group for a carboxyl group includes, for example, C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, tert-butyl etc.), phenyl, trityl, silyl and the like, each of which may be optionally substituted. As such a substituent, a halogen atom (e.g. fluorine, chlorine, bromine, iodine etc.), formyl, C_{1-6} alkyl-carbonyl (e.g. acetyl, ethylcarbonyl, butylcarbonyl etc.), a nitro group or the like is used and the number of substituents is about 1 to 3.

A protecting group for a hydroxy group includes, for example, C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, tert-butyl etc.), phenyl, C_{7-10} aralkyl (e.g. benzyl etc.), formyl, C_{1-6} alkyl-carbonyl (e.g. acetyl, ethylcarbonyl etc.), phenyloxycarbonyl, benzoyl, C_{7-10} aralkyl-carbonyl (e.g. benzylcarbonyl etc.), pyranyl, furanyl, silyl and the like, each of which may be optionally substituted. As such a substituent, a halogen atom (e.g. fluorine, chlorine, bromine, iodine etc.), C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl etc.), phenyl, C_{7-10} aralkyl (e.g. benzyl etc.), a nitro group or the like is used and the number of substituents is about 1 to 4.

A method of removing a protecting group may be a method known per se or the similar method, and for example,

a method comprising treatment with acid, base, reduction, ultraviolet light, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate or the like is used.

In addition, in each reaction of the process for preparing the compound [I] or a salt thereof and each reaction for synthesizing the starting compounds described above, a generally known solvent may be used during the reaction.

A generally known solvent includes, for example, ethers such as tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane and 1,4-dioxane; esters such as ethyl acetate and butyl acetate; aromatic hydrocarbons such as benzene and toluene; aromatic heterocyclic compounds such as pyridine and lutidine; amides such as N,N-dimethylformamide and N-methylpyrrolidone; halides such as chloroform and methylene chloride; alcohols such as methanol, ethanol, 2-propanol and 2,2-dimethylethanol; hydrocarbon compounds such as hexane, heptane and petroleum ether; carboxylic acids such as formic acid and acetic acid; water; and the like.

A solvent used in the reaction may be a single solvent or a mixture of 2 to 6 solvents.

The reaction may be also performed in the presence of a base such as amines such as triethylamine, N,N-

diisopropylamine, pyridine or N-methylmorpholine, sodium hydroxide, potassium carbonate or the like.

The reaction may be also performed in the presence of an acid such as hydrochloric acid, sulfuric acid, acetic acid or the like.

The compound represented by the formula [I] or a salt thereof obtained by the above methods can be isolated or purified by a conventional separation means such as recrystallization, distillation, chromatography or the like. When the compound represented by the formula [I] of the present invention thus obtained is in the free form, it can be converted into a salt form by a method known per se or the similar method (e.g. neutralization, etc.). Conversely, when the compound is obtained as a salt, it can be converted into the free form or another salt by a method known per se or the similar method. When the resulting compound is in the racemic form, it can be separated into the d-form and the l-form by a conventional optical resolution means.

The starting compounds of the compound represented by the formula [I] or a salt thereof may be also in a salt form similar to a salt of the compound represented by the formula [I], but the kind of the salt is not particularly limited as long as the reaction is not disturbed.

The compound represented by the formula [II] or a

derivative thereof can be prepared by, for example, a method described in EPA567026, WO95/21834 (PCT application based on Japanese Patent Application No. 6-15531), EPA645377 (application based on Japanese Patent Application No. 6-229159), EPA645378 (application based on Japanese Patent Application No. 6-229160) or JP-A 9-136880, or the similar method.

Since the compound represented by the formula [I] or a salt or a prodrug thereof (hereinafter sometimes referred to merely as the compound (I), including a salt thereof and a prodrug thereof) is low toxic and has squalene synthase inhibitory activity, LDL cholesterol lowering activity, triglyceride lowering activity, lipid lowering activity, non-HDL cholesterol lowering activity and HDL cholesterol level elevating activity, it is useful as a safe medicament for prevention or treatment of hyperlipemia such as hypercholesterolemia, hypertriglyceridemia or hypoHDLemia in a mammal (e.g., mouse, rat, rabbit, dog, cat, cattle, pig, monkey, human and the like) and is also useful for prevention or treatment of metabolic syndrome. Moreover, the compound is useful as a safe medicament for prevention or treatment of kidney disease such as nephritis or nephropathy, arteriosclerosis, ischemic disease, heart infarction, angina pectoris, heart failure, aneurysm, cerebral arteriosclerosis, cerebral apoplexy, transient

ischemic stroke, brain infarction, peripheral arteriosclerosis, intermittent claudication, thrombosis, hypertension, osteoporosis, diabetes (e.g., insulin resistance-dependent type and the like), diabetic complications (e.g. diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, diabetic angiopathy and the like), pancreatic disorder, or restenosis after percutaneous coronary plasty (PTCA) or stent placement.

Hereinafter the utility of the present invention is explained in detail.

The compound (I) has superior triglyceride lowering activity and cholesterol lowering activity as well as biological characteristics thereof, and is specifically suitable for treatment or prevention of hyperlipemia, in particular hypertriglyceridemia, hyperlipoproteinemia and hypercholesterolemia, as well as metabolic syndrome and atherosclerotic vascular lesion arising therefrom and secondary disease thereof such as coronary artery disease, cardiac infarction, angina pectoris, brain infarction, brain ischemia, intermittent claudication, peripheral arteriosclerosis, gangrene and the like.

For treatment of these diseases, the compound (I) may be used alone or may be used in combination with other drug ingredients such as a lipid lowering agent, a cholesterol lowering agent, an HDL level elevating agent or a

cholesterol absorption inhibitor (administered simultaneously or administered at a certain interval). In this case, these compounds are preferably administered as oral preparations (including intraoral disintegrating tablets) or they may be optionally administered in the form of suppository as rectal preparations. In this case, possible ingredients for the combination use include, for example, a $PPAR_{\alpha}$ agonist such as fibrates [e.g., Clofibrate, Benzafibrate, Gemfibrozil, Fenofibrate, Wy-1463, GW9578 and the like]; and a cholesterol lowering agent such as nicotinic acid and a derivative and analogue thereof [e.g., Acipimox and Probucol], a bile acid-binding resin [e.g., Cholestyramine, Colestipol and the like], a compound that suppresses absorption of cholesterol [e.g., Ezetimibe, Sitosterol, Neomycin and the like], a compound that inhibits biosynthesis of cholesterol [e.g., an HMG-CoA reductase inhibitor such as Lovastatın, Simvastatin, Pravastatin, Atorvastatin, ZD-4522 (Rosuvastatin), Itavastatin and the like], a squalene epoxidase inhibitor [e.g., NB-598 and an analogue compound thereof and the like] or an HDL level elevating agent due to ınhibition of cholesterol ester-transporting protein [e.g. JTT-705, CP-529-414 and the like]. In addition, a combination with an acyl-Coenzyme A cholesterol acyltransferase (ACAT) inhibitor (e.g. melinamıde etc.) or a lipid rich plaque

regressing agent (e.g. compounds described in WO 02/06264, WO 03/059900 etc.) is possible. Further, a combination with a body fat lowering agent such as a pancreatic lipase inhibitor (e.g.orlistat etc.) is also possible.

Another possible ingredient for the combination use includes an oxide squalene-lanosterol cyclase inhibitor, for example, a decalin derivative, an azadecalin derivative or an indan derivative.

In particular, by combining with an HMG-CoA reductase inhibitor, myalgia and myolysis which are also the side effect of an HMG-CoA reductase inhibitor may be alleviated. Further, this combination not only has lipid lowering activity but also is effective against osteoporosis and Alzheimer's disease, and may improve the prognosis of ischemic disease (cerebral apoplexy, cardiac infarction or the like).

In addition, the compound (I) is suitable for treatment of disease associated with hyperchylomicronemia, for example, acute pancreatitis. Regarding the mechanism of onset of pancreatitis, it is said that chylomicrons cause microembolization in a pancreatic capillary blood vessel, or hyperchylomicronemia results in increase in production of free fatty acid by digestion of triglyceride with pancreatic lipase and then the free fatty acid stimulates strongly a local place, whereby pancreatitis is

developed. Therefore, since the compound (I) has triglyceride lowering activity, it can treat pancreatitis and it can be used for treating pancreatitis alone or in combination with a known therapy. For treatment of this disease, the compound (I) can be administered orally or topically and it can be used alone or in combination with a known active compound. In this case, ingredients which can be combined include, for example, aprotinin (Trasylol), gabexate mesilate (FOY), nafamostat mesilate (Fusan), citicoline (Nicoline), urinastatin (Miraclid) and the like for anti-enzymatic therapy. For the purpose of alleviation of pain, an anticholinergic agent, a non-narcotic analgesic or a narcotic is also used.

A further notable example of application of the compound (I) is application for secondary hyperlipemia. The disease includes diabetes, hypothyroidism, nephrotic syndrome or chronic renal failure and the like, and hyperlipemia onsets subsequent to these diseases. In many cases, hyperlipemia aggravates these diseases, namely, forms a vicious circle. In view of lipid lowering activity, the compound (I) is also suitable for treatment or prevention of development of these diseases, and in this case, it can be administered alone or in combination with the medicaments listed below.

Diabetes treating drugs: Kinedak, Penfil, Humalin,

Euglucon, Glimicron, Daonil, Novolin, Monotard, insulins, Glucobay, Dimelin, Rastinon, bacilcon, Deamelin S, iszilins; ınsulin sensitizers (thiazolidine and non-thiazolidine PPAR agonists: pioglitazone, Avandia, KRP-297, TAK-559, MCC-555 etc., isoxazolidine drugs: JTT-501 etc.), biguanide drugs (e.g. mitiglinide etc.), insulin secretion promoting drugs (e.g. sulfonylurea agents etc.), α-glucocidase inhibitors (e.g. voglibose etc.), β_3-agonists (e.g. TAK-677 etc.), insulin preparations etc.;

Hypothyroidism treating drugs: dried thyroid (Thireoid), levothyroxine sodium (Thyradin S), liothyronine sodium (Thyronine, Thyronamin);

Nephrotic syndrome terating drugs: prednisolone (Predonine), prednisolone sodium succinate (Predonine), methylprednisolone sodium succinate (Solu-Medrol), betamethasone (Lynderon);

Anticoagulant therapy agents: dipyridamole (Persantin), dilazep hydrochloride (Comelıan) and the like;

Chronic renal failure terating drugs: diuretic [e.g., furosemide (Lasix), bumetanide (Lunetoron), azosemide (Diart) etc.], ACE inhibitors [e.g. enalapril maleate (Renivace) etc.], angiotensin II receptor antagonists [e.g. candesartan cilexetil (Blopress), losartan potassium (Nu-lotan), valsartan (Diovan), irbesartan etc.], Ca antagonists (maninhiron), α receptor blockers and the like.

In combination with these drugs, the compound (I) can be preferably orally administered.

Since hyperlipemia aggravates arterial sclerosis and causes hypertension, the compound (I) is suitable for treatment or prevention of hypertension, and in this case, the compound (I) can be administered alone or in combination with the medicaments listed below. In this case, the possible combination includes combinations with, for example, angiotensin-II antagonists [e.g., losartan potassium (Nu-Lotan), candesartan cilexetil (Blopress) and the like], ACE inhibitors [e.g., enalapril maleate (Renivace), lisinopril (Zestril, Longes), delapril hydrochloride (Adecut), captopril and the like], calcium antagonists [e.g., amlodipine besylate (Amlodin, Norvasc), manidipine hydrochloride (Calslot) and the like], hypotensive diuretic, α receptor blockers, β receptor blockers and the like.

A further notable indication of the compound (I) is osteoporosis accompanied by increase of blood cholesterol. Because of the superior lipid lowering activity, the compound (I) can be used for treatment or prevention of osteoporosis accompanied by increase of blood cholesterol, and in this case, the compound (I) can be administered alone or in combination with the medicaments listed below. The possible combination includes combinations with a sex

hormone and associated drugs [e.g., an estrogen preparation, ipriflavone (Osten), raloxifene, osaterone, tibolone and the like], a bone resorption inhibitor such as calcitonins, vitamin D preparations [e.g., alfacalcidol, calcitriol and the like], bisphosphonates (e.g., etidronate, clodronate and the like) and the like, a bone formation-accelerating agent such as fluorine compound, PTH and the like.

Further possible application of the compound (I) is use for suppression of thrombus formation. Since blood triglyceride level and Factor VII that involves in blood clotting have a positive correlation, and triglyceride is decreased and clotting is suppressed by intake of ω-3 fatty acid, hypertriglyceridemia accelerates thrombus formation. Furthermore, since the VLDL of a hyperlipemia patient increased secretion of a plasminogen activator inhibitor from a vascular endothelial cell more strongly than that of a person having normal blood lipid, it is also thought that triglyceride (hereinafter referred as TG) decreases the fibrinolysis ability. Therefore, in view of the TG lowering activity, the compound (I) is suitable for prevention or treatment of thrombus formation. In this case, the compound can be used alone or in combination with the known therapeutic agents listed below, preferably for oral administration.

Thrombus formation preventing or treating drugs: blood

coagulation inhibitors [e.g., heparin sodium, heparin calcium, warfarin calcium (Warfarin) etc.], thrombolytic drugs [e.g., urokinase], antiplatelet drugs [e.g., aspirin, sulfinpyrazone (Anturan), dipyridamole (Persantin), ticlopidine (Panaldine), cilostazol (Pletal), clopidogrel etc.].

In addition, the compound (I) has superior high-density lipoprotein-cholesterol level elevating activity and is low toxic. Therefore, these compounds and salts thereof can be used safely as, for example, an agent for prevention or treatment of primary low or high-density lipoprotein-cholesterolemia, Tangier disease or the like, as well as an agent for prevention or treatment of cardiac infarction, atherosclerotic disease, hyperlipemia, mixed-type lipid abnormality, diabetes, diabetic complication or the like and can be used for preventing or treating arteriosclerosis, hyperlipemia, hypertension, diabetes, diabetic complication, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, arrhythmia, peripheral vascular disease, thrombosis, pancreatic disorder, ischemic cardiac disease, brain ischemia, sequela of cardiac infarction, heart failure, cardiac valvular disease or Alzheimer's disease, in a mammal (e.g., mouse, rat, hamster, rabbit, cat, dog, cattle, horse, sheep, monkey, human and the like). In addition, the compound (I) is suitable for

treating and preventing hypoHDLemia (including primary hypoHDLemia), Tangier disease, and ischemic heart disease that is developed frequently in a diabetic patient after menopause. In addition, the compound (I) is particularly suitable for treating and preventing hyperlipemia, in particular, hypertriglyceridemia, hyperlipoproteinemia and hypercholesterolemia, as well as atherosclerosis vascular lesion arising therefrom and the secondary diseases thereof such as coronary artery disease, cerebral ischemia, aneurysm, cerebral arteriosclerosis, peripheral arteriosclerosis, intermittent claudication, gangrene and the like

As a further notable example for application of the compound (I), prevention or treatment of Alzheimer's disease is exemplified. It has been known that increase of blood choresterol is a risk factor of Alzheimer's disease. The compound (I) can be used for prevention or treatment of Alzheimer's disease due to its superior high density lipoprotein-cholesterol level elevating activity and lipid lowering activity, and when the compound (I) is used for such purpose, it can be administered alone or in combination with the following drugs. In this case, the possible combination includes combinations with an acetylcholinesterase inhibitor (e.g., Aricept, Excelon and the like), an amyloid β-production or secretion inhibitor

(e.g., a γ or β secretase inhibitor such as JT-52, LY-374973 and the like, or SIB-1848 and the like), an amyloid β coagulation inhibitor (e.g., PTI-00703, BETABLOC (AN-1792) and the like) and the like.

In addition, since the compound (I) has blood glucose lowering activity and shows blood glucose lowering activity in a rat suffering from endomorphic diabetes, it improves insulin resistance. It is, in view of its biological characteristics, especially suitable for prevention or treatment of hyperglycemia and the secondary disease arising therefrom such as complications observed in the diabetic nephropathy and renal failure stage, circulatory disease such as anaemia, bone metabolism abnormality, vomiting, nausea, anorexia and diarrhea, nervous symptoms such as neuropathy, diabetic neuropathy, diabetic retinopathy, diabetic vascular disorder, as well as insulin resistance and diseases arising therefrom such as hypertension and impaired glucose tolerance and the secondary disease such as cardiac disease, cardiac failure, ischemic cardiac disease, cerebral ischemia, intermittent claudication and gangrene.

In treatment of these diseases, the high-density lipoprotein-cholesterol level elevating agent of the present invention may be used alone for prevention or treatment, or may be used in combination with other blood

glucose lowering drugs or hypotensive drugs. In this case, these compounds are preferably administered as oral preparations (including intraoral disintegrating tablets). Alternatively, if necessary, the compounds may be administered as rectal preparations in the form of suppository. The ingredients that can be combined in this case include (1) an insulin preparation (e.g., human insulin and the like), (2) a sulfonylurea agent (e.g., glibenclamide, gliclazide, glimepiride and the like), (3) an α-glucosidase inhibitor (e.g., voglibose, acarbose and the like), (4) an insulin sensitizer (e.g., pioglitazone, rosiglitazone and the like), (5) an aldose reductase inhibitor (e.g., Epalrestat, Torestat and the like), and a glycation inhibitor (e.g., aminoguanidine and the like).

A combination with a gynecologic disease treating drug (a climacteric disorder treating drug (conjugated estrogen, estradiol, testosterone enanthate, estradiol valerate and the like), a breast cancer treating drug (tamoxifen citrate and the like), a endometriosis and hysteromyoma treating drug (leuprorelin acetate, danazol and the like) or the like, or a combination with such a drug and a diabetes treating drug is also possible.

Furthermore, a combination with a hypotensive agent is possible, and the agent includes, for example, (1) a diuretic (e.g., furosemide, spironolactone and the like),

(2) a sympathetic nerve inhibitor (e.g., atenolol and the like), (3) an angiotensin II receptor antagonist (e.g., losartan, candesartan cilexetil, valsartan, irbesartan, olmesartan and the like), (4) an angiotensin I converting enzyme inhibitor (e.g., enalapril maleate, delapril hydrochloride and the like), (5) a calcium antagonist (e.g., nifedipine, manidipine hydrochloride, amlodipine besylate and the like) and the like.

In addition, a combination with a chronic cardiac failure treating drug is possible, and the drug includes, for example, (1) a β receptor blocker, (2) an ACE inhibitor [e.g. enalapril maleate (renivace), lisinopril (longes, zestril etc.)], (3) an angiotensin II receptor antagonist [e.g. candesartan cilexetil (blopress), valsartan, losartan etc.], (4) an aldosterone antagonist (spironolactone, eplerenone), (5) an endothelin antagonist, (6) a Na-H exchange inhibitor, (7) a Na-Ca exchange inhibitor, (8) a MCC-135 and the like.

The compound (I) has superior skeletal muscle protecting activity. That is, the compound (I) exhibits treating of preventing effect against condition in which skeletal muscle is necrosed or colliquated, caused by various factors such as ischemia, effort, excessive exercise, trauma (bruise, skeletal muscle bleeding, electric shock), burn, malignant hyperthermia, malignant

syndrome, metabolic myopathy, inflammatory myopathy, muscular dystrophy, infection, intoxication, metabolism abnormality and hyperthermia. More specifically, the compound (I) protects skeletal muscle from cell disorder resulting from the above factors. In addition, the compound (I) has treating or preventing effect against myalgia resulting from cytotoxicity of other drugs (e.g. HMG-CoA reductase inhibitors, cyclosporin, fibrate drugs etc.) and further, rhabdomyolysis in a serious case, etc..

In particular, the compound (I) exhibits superior treating or preventing effect against myalgia induced by a HMG-CoA reductase inhibitor and further, serious rhabdomyolysis, and inhibits decrease of geranylgeranylpyrophosphate in a muscular cell induced by a HMG-CoA reductase inhibitor (e.g. atorvastatin, lovastatin, simvastatin, pravastatin, rosuvastatin, itavastatin, fluvastatin, cerivastatin, pitavastatin etc.).

The compound (I) has superior skeletal muscle protecting activity and is low toxic. Therefore, the agent of the present invention can be safely used, for example, as an agent for preventing or treating rhabdomyolysis, myoglobinuria associated with rhabdomyolysis, or myalgia, in a mammal (e.g. mouse, rat, hamster, rabbit, cat, dog, cow, horse, sheep, monkey, human etc.).

The compound (I) has superior ubiquinone increasing

activity, and preventing or treating effect against and inhibiting effect of progression of organ dysfunction and organ failure, and thus, is useful as an agent for preventing or treating and for inhibiting progression of diseases based on this pharmacological activity. Herein, organ dysfunction includes hypofunction of various organs and complications thereof and, inter alia, preferred is ischemic organ dysfunction. That is, the compound of the present invention can prevent cell death caused by ischemia or the like and can protect the function of a cell and an organ, and thus, it can be also used as an agent for maintaining the function of an organ, an agent for protecting an organ, an inhibitor of organ cell death, or the like. Specifically, the compound of the present invention can prevent or treat heart hypofunction (including damage of cardiac muscle), brain hypofunction and pancreatic hypofunction resulting from various factors (in particular, based on ischemia) and the failure of each organ and can inhibit progress to death.

In addition, organ dysfunction may be organ dysfunction resulting from diseases such as arteriosclerotic diseases (cardiac infarction, angina pectoris, brain infarction, cerebral hemorrhage etc.) including ischemic cardiac disease, or may be organ dysfunction occurring during or after an operation or

transplantation of an organ. Further, the agent of the present invention is also useful for inhibiting progression, improving prognosis, and preventing secondary development and recurrence of diseases (in particular, ischemic disease such as ischemic cardiac disease or brain infarction) which are causes of the aforementioned organ dysfunctions.

Herein, the organ includes, for example, brain, liver, kidney, heart, spleen, pancreas, eye (retina), and nervous tissue (central nervous tissue, peripheral nervous tissue etc.); preferably, peripheral nervous tissue and, inter alia, preferred are heart and nervous tissue.

Having both of squalene synthase inhibitory activity and ubiquinone increasing activity allows application of the agent to the prognosis of ischemic disease or the like in brain, heart, kidney, nervous tissue, pancreas or the like. For example, in the case of a brain (nervous tissue), inhibiting the progress to a coma, maintaining consciousness or life-prolonging becomes possible, and Parkinson's disease or Alzheimer's disease resulting from central neurodegenerative disease can be treated. In addition, treatment of numbness of hands and feet, imperception, pain, thermal sensitivity abnormality, ulcer, or nervous hyporeflexia resulting from peripheral neuropathy becomes possible. In the case of a heart, treatment of cardiac failure or arrhythmia, or life-

prolonging becomes possible. In the case of kidneys, inhibiting the progress to dialysis or renal transplantation, or life-prolonging becomes possible.

The compound of the present invention has superior ubiquinone increasing activity and preventing or treating effect against organ dysfunction or organ failure, and is low toxic. Therefore, the compound of the present invention can be safely used as an agent for preventing or treating cardiac infarction, arteriosclerotic diseases, hyperlipemia, brain infarction, cerebral hemorrhage, neurodegenerative disease or diabetes, or diabetic complications, in addition to an agent for preventing or treating and an agent for inhibiting progression of organ dysfunction or organ failure.

The compound (I) can be used for treating or preventing arteriosclerosis, hyperlipemia, mixed-type lipid abnormality, diabetes, diabetic complications, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, arrhythmia, peripheral vascular disease, thrombosis, pancreatic disorder, ischemic heart disease, CHD (coronary heart diseases), cerebral ischemia, cardiac infarction, the sequelae of cardiac infarction, heart valvular disease, or Alzheimer's disease. In addition, the compound (I) can be used for preventing or treating cerebral infarction; cerebral hemorrhage; pollakiuria, urinary incontinence or

deteriorated excretion of urinary bladder based on neuropathy; Parkinson's disease based on neurodegenerative disease; and cerebral vascular dementia, in addition to cardiac failure and renal failure. The compound (I) is also useful for inhibiting death caused by these diseases or life-prolonging.

Furthermore, ubiquinone has been reported to activate the UCP (uncoupling protein) function. Therefore, the compound (I) is useful for preventing or treating obesity and is suitable for preventing or treating impaired glucose tolerance, diabetes, insulin resistance, hypertension, hyperlipemia or the like associated with obesity.

Since the compound (I) has both of squalene synthase inhibiting activity and ubiquinone increasing activity in addition to lipid metabolism improving activity such as cholesterol lowering activity, triglyceride lowering activity and high-density lipoprotein-cholesterol (HDL) level elevating activity, it can be extremely advantageously used for preventing or treating organ dysfunction or organ failure, inter alia, organ dysfunction or organ failure resulting from diseases such as arteriosclerotic disease (cardiac infarction, angina pectoris, cerebral infarction, cerebral hemorrhage etc.) including ischemic cardiac disease. In addition, since the compound (I) has ubiquinone increasing activity in addition

to lipid lowering activity, for example, it can treat ischemic cardiac disease, prevent or treat more serious cardiac failure, and inhibit progress from cardiac failure to death, and thus it is extremely useful as compared with a lipid lowering agent having no ubiquinone increasing activity. In addition, regarding other organs such as brain, kidney and nervous tissue, the compound (I) having ubiquinone increasing activity in addition to lipid lowering activity is excellent in terms of being capable of preventing or treating organ or tissue failure in addition to organ dysfunction, and also has life-prolonging effect.

When the compound (I) is applied to the aforementioned various diseases, it can be used in combination with biologics (e.g. antibodies, vaccine preparations, etc.). Alternatively, the compound (I) can be applied as a combination therapy in combination with genetic therapy. The antibodies and vaccine preparations include vaccine preparations directed to angiotensin II, vaccine preparations directed to CETP, CETP antibodies, TNF α antibodies and antibodies directed to other cytokine, amyloid β vaccine preparations, and 1-type diabetes vaccines (DIAPEP-277 of Peptor Company, etc.), as well as antibodies or vaccine preparations directed to cytokine, renin-angiotensin enzymes and the products thereof, antibodies or vaccine preparations directed to enzymes or

proteins involved in blood lipid metabolism, antibodies or vaccines relating to enzymes or proteins involved in coagulation or fibrinogenolysis system in blood, and antibodies or vaccine preparations directed to proteins involved in glucose metabolism or insulin resistance. The genetic therapy includes therapies using genes associated with cytokine, renin-angiotensin enzymes and the products thereof, therapies using DNA decoy such as NFκB decoy, therapies using antisense, therapies using genes associated with enzymes or a proteins involved in blood lipid metabolism (e.g. genes associated with metabolism, excretion or absorption of cholesterol, triglyceride, HDL-cholesterol or blood phospholipid), therapies using genes associated with enzymes or proteins (e.g. growth factors such as HGF, VEGF etc.) involved in vascularization therapy for peripheral vascular obstruction, therapies using genes associated with proteins involved in glucose metabolism or insulin resistance, and antisense for cytokine such as TNF. Alternatively, the compound (I) can be used in combination with various organs regeneration method such as heart regeneration, kidney regeneration, pancreas regeneration or revascularization, or vascularization therapy utilizing transplantation of marrow cells (marrow mononuclear cell, marrow stem cell etc.).

When the compound (I) is combined with other drugs

upon application to the aforementioned respective diseases, these active ingredients may be administered as a combined agent obtained by formulating them in one preparation.

The compound (I) can be used orally or parenterally via injection, infusion, inhalation, rectal administration or local administration, and can be used as it is or as a pharmaceutical composition (e.g. powders, granules, tablets, pills, capsules, injections, syrups, emulsions, elixirs, suspensions, solutions etc.). That is, at least one compound (I) can be used alone or as a mixture of a pharmaceutically acceptable carrier (adjuvant, excipient, additive and/or diluent).

For the medicine of the present invention, the compound (I) which is the active ingredient may be administered as bulk powder, but usually, is administered in a form prepared by a conventional method appropriately using an appropriate amount of a conventional pharmaceutical carrier, for example, an excipient (e.g. calcium carbonate, kaolin, sodium hydrogen carbonate, lactose, starch, crystalline cellulose, talc, granulated sugar, porous substances etc.), a binder (e.g. dextrin, gums, alcoholated starch, gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose, pullulan etc.), a disintegrant (e.g. carboxymethylcellulose potassium, croscarmerose sodium, crospovidone, low-substituted

hydroxypropylcellulose, partially α-starch etc.), a lubricant (e.g. magnesium stearate, calcium stearate, talc, starch, sodium benzoate etc.), a coloring agent (e.g. tar dye, caramel, iron sesquioxide, titanium dioxide, riboflavins), a corrigent (e.g. sweetener, flavor etc.), a stabilizer (e.g. sodium sulfite etc.) and a preservative (e.g. parabens, sorbic acid etc.). The medicine of the invention including the aforementioned agent usually contains the compound (I) in an effective amount for treating and preventing disease. The content of the compound of the formula (I) in the medicine of the present invention is usually 0.1 to 100% by weight of the total preparation. The medicine used in the present invention may contain drug ingredients other than the compound (I) as an active ingredient, said ingredients are not particularly limited as long as the object of the invention is achieved, and can be used at an appropriate combination ratio. Specific examples of the dosage form include tablets (including sugar-coated tablets, film-coated tablets), pills, capsules, granules, fine granules, powders, syrups, emulsions, suspensions, injections, sustained-release injections, inhalants, and ointments. Such preparations are prepared according to a conventional method (e.g. a method described in Japanese Pharmacopoeia).

Specifically, a tablet can be produced by granulating

the compound (I) alone or a uniform mixture of the compound (I) and an excipient, a binder, a disintegrant or another suitable additive by a suitable method, followed by addition of a lubricant or the like, and then compressing the resulting granule; by compressing directly the compound (I) alone or a uniform mixture of the compound (I) and an excipient, a binder, a disintegrant or another suitable additive; or by compressing a granule prepared in advance alone or a uniform mixture of the granule and a suitable additive. The present tablet may contain a coloring agent, a corrigent or the like if necessary. The present tablet may be also coated with a suitable coating agent. An injection can be prepared by dissolving, suspending or emulsifying a certain amount of the compound (I) in water for injection, physiological saline, Ringer's solution or the like for an aqueous solvent, or in a conventional vegetable oil or the like for a non-aqueous solvent to obtain a certain amount of the resulting injection, or by putting a certain amount of the compound (I) into a container for injection and then sealing it.

A carrier for an oral preparation includes substances used conventionally in the drug preparation art such as starch, mannitol, crystalline cellulose,carboxymethylcellulose sodium, etc.. A carrier for injection includes distilled water, a physiological

saline, a glucose solution and an infusion solution. Additionally, other additives used for general preparation may be suitably added.

The medicine of the present invention can be also used as a sustained-release preparation. The sustained-release preparation may be a microcapsule (e.g. microsphere microcapsule, microparticle etc.) as it is prepared by a drying-in-water method (o/w method, w/o/w method, etc.), a phase separation method, spray drying or a similar manner thereto, or a preparation obtained by formulating the microcapsule or a pharmaceutical composition in sphere form, needle form, pellet form, film form or cream form, as raw material, into various dosage forms. The dosage form includes a parenteral preparation (e.g., an injection or an implant for intramuscular, subcutaneous, organ, etc.; an intramucosal agent for nasal cavity, rectum, uterus, etc., etc.), and an oral preparation (e.g., hard capsule, soft capsule, granule, powder, suspension, etc.).

When the sustained-release preparation is an injection, the sustained-release injection is prepared by dispersing the microcapsule in a dispersing agent (e.g., surfactants such as Tween 80, HCO-60, etc.; polysaccharides such as carboxymethylcellulose, sodium arginate, sodium hyaluronate, etc.; protamine sulfate, polyethyleneglycol, etc.), preservatives (e.g., methylparaben, propylparaben, etc.),

isotonizing agents (e.g., sodium chloride, mannitol, sorbitol, glucose, etc.), local anesthetics (e.g., xylocaine hydrochloride, chlorobutanol, etc.), etc. to give an aqueous suspension, or by dispersing the microcapsule in vegetable oil (e.g., sesame oil, corn oil, etc.) or a mixture thereof with phospholipids (e.g., lecithin, etc.) or middle chain fatty acid triglycerides (e.g., Miglyol 812, etc.) to give an oily suspension.

When the sustained-release preparation is a microcapsule, its average particle diameter is about 0.1 to about 300 μm, preferably about 1 to about 150 μm, further preferably about 2 to about 100 μm.

When the microcapsule is formulated into a sterile preparation, there are a method comprising sterilizing the whole steps of preparation, a method comprising sterilizing using gamma ray, a method comprising adding an antiseptic, etc., but the method is not specifically limited.

The medicine of the present invention can be formulated into a preparation according to a conventional method. Such preparation can be usually prepared by mixing/kneading an active ingredient with an additive such as an excipient, a diluent or a carrier. The "parenteral", when used herein, includes subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection and infusion. An injectable

preparation, for example, a sterile aqueous or oily suspension for injection may be prepared using a suitable dispersing agent or wetting agent and a suitable suspending agent by a method known in the art. The sterile injectable preparation may be a sterile injectable solution or suspension in a diluent or a solvent, which is non-toxic and can be administered parenterally, for example, an aqueous solution. An acceptable vehicle or solvent which can be used includes water, Ringer's solution, and an isotonic sodium chloride solution. A sterile involatile oil may be also usually used as a solvent or a suspending solvent. For this, any involatile oil or fatty acid can be used, including synthetic or semisynthetic fatty oil or fatty acid, and natural or synthetic or semisynthetic mono- or di- or triglycerides.

A suppository for rectal administration can be prepared by mixing the drug with an appropriate non-stimulative additive, for example, an additive which is solid at the normal temperature but is liquid at the temperature of an intestine tract, is melted in a rectum and releases a drug, such as cocoa butter or polyethylene glycol.

Examples of a solid dosage form for oral administration include the aforementioned powders, granules, tablets, pills and capsules, etc.. A preparation in such

dosage form can be prepared by mixing and/or kneading an active ingredient compound with at least one additive, for example, sucrose, lactose, cellulose sugar, mannitol (D-mannitol), maltitol, dextran, starches (e.g. corn starch), microcrystalline cellulose, agar, alginates, chitins, chitosans, pectins, tragacanths gums, gums arabic, gelatins, collagens, caseins, albumin, and synthetic or semisynthetic polymers or glycerides. Such dosage forms can contain further additives as usual, and said additives include an inert diluent, a lubricant such as stearic acid and magnesium stearate, a preservative such as parabens and sorbic acid, an antioxidant such as ascorbic acid, α-tocopherol and cysteine, a disintegrant (e.g. croscarmerose sodium), a binder (e.g. hydroxypropylcellulose), a thickener, a buffer, a sweetener, a flavor, and a perfume. Tablets and pills may be prepared by further enteric coating. Solutions for oral administration include pharmaceutically acceptable emulsions, syrups, elixirs, suspensions and solutions. They may contain an inert diluent which is conventionally used in the art, for example, water and, if necessary, additives. These oral solutions can be prepared according to a conventional method, for example, by mixing an active ingredient compound and an inert diluent and, if necessary, other additives.

An oral preparation may contain, depending on the dosage form, usually about 0.01 to 99 W%, preferably about 0.1 to 90 W%, usually about 0.5 to 50% of the active ingredient compound of the present invention.

The dose for a particular patient is determined depending on the age, weight, general health condition, sex, diet, administration time, administration method, secretion rate, combination of drugs, and extent of symptom of a patient to be treated, or considering them and other factors.

The compound of the present invention has squalene synthase inhibitory activity, cholesterol lowering activity and triglyceride lowering activity, and has high selectivity for transition to a target organ and a wide safety margin. Thus, the compound of the present invention is useful for preventing or treating hyperlipemia as a lipid lowering agent and is also useful for preventing or treating arteriosclerosis.

A medicine containing the compound (I) of the present invention is low toxic and can be safely used. The daily dose of the medicine varies depending on the condition and weight of a patient, the kind of a compound and the administration route, etc. For example, when the medicine is used as an agent for preventing or treating hyperlipemia, the daily dose for an adult (body weight about 60 kg) is

about 1 to 500 mg, preferably about 10 to 200 mg of the active ingredient [the compound (I)] in the case of an oral preparation, and is about 0.1 to 100 mg, preferably about 1 to 50 mg, usually about 1 to 20 mg of the active ingredient in the case of a parenteral preparation. No toxicity is found within such a range.

The following Examples, Preparation Examples and Experimental Examples will further explain the present invention in detail, but the present invention is not limited to them.

^{1}H-NMR spectrum was measured by Varian Gemini 200(200MHz)-type or 300(300MHz)-type spectrometer using tetramethylsilane as an internal standard. All δ values are shown in ppm. The numerical value denoted for a mixed solvent is the mixing ratio of respective solvents based on volume unless otherwise indicated. The % means % by weight unless otherwise indicated. The ratio of elution solvents for silica gel chromatography is based on volume unless otherwise indicated. The room temperature (normal temperature), as used herein, is from about 20°C to about 30°C.

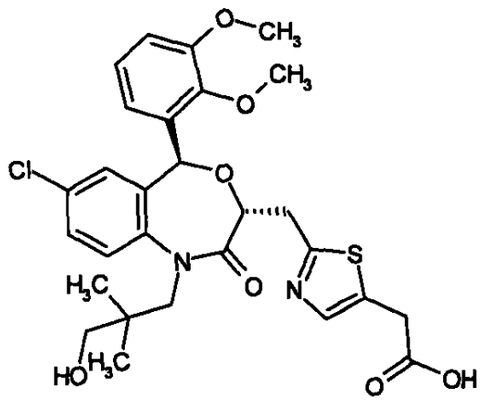
Respective symbols in Examples have the following meanings:

Ac: acetyl, Pr: n-propyl, Me: methyl, Bu: n-butyl, Et:

ethyl, ^{i}Pr: isopropyl, Et_2O: diethyl ether, DMF: N,N-dimethylformamide, DMSO: dimethyl sulfoxide, THF: tetrahydrofuran, s: singlet, d: doublet, t: triplet, q: quartet, dd: double doublet, dt: double triplet, m: multiplet, br: broad, J: coupling constant

Example 1

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetic acid



(1) Carbonyldiimidazole (10.2 g, 63.1 mmol) was added to a suspension of 2-(tert-butoxycarbonylamino)acetic acid (10 g, 57.1 mmol) in THF (100 ml) and the mixture was stirred at room temperature for 2 hours. To the reaction solution were added magnesium chloride (5.4 g, 57.1 mmol) and potassium monoethylmalonate (9.7 g, 57.1 mmol) and the mixture was stirred at 60°C for 1 hour. The mixture was filtered to remove insoluble substances. The filtrate was

diluted with ethyl acetate (200 ml), washed with 1N hydrochloric acid, an aqueous saturated sodium hydrogen carbonate solution and an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (2:1)] to obtain ethyl 4-(tert-butoxycarbonylamino)-3-oxobutanoate (11.9 g, 48.5 mmol, 85%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J = 7.4 Hz), 1.45 (2H, s), 3.87 (2H, s), 3.96 (3H, s), 4.21 (2H, q, J = 7.2 Hz), 7.08 (1H, d, J = 8.7 Hz), 7.39 (9H, s), 3.49 (2H, s), 4.14 (2H, d, J = 5.8 Hz), 4.21 (2H, q, J = 7.4 Hz), 5.15-5.24 (1H, br).

(2) 4N HCl solution in ethyl acetate (50 ml) was added to a solution of ethyl 4-(tert-butoxycarbonylamino)-3-oxobutanoate (11 g, 44.8 mmol) obtained in Example 1-(1) in acetic acid (6 ml) and the mixture was stirred at room temperature for 30 minutes. The reaction solution was concentrated under reduced pressure and the residue was crystallized from ethyl acetate to obtain ethyl 4-amino-3-oxobutanoate hydrochloride (7.9 g, 43.5 mmol, 97%) as colorless powder.

^{1}H-NMR (CD_3OD) δ: 1.27 (3H, t, J = 7.2 Hz), 3.69 (2H, s), 4.124 (2H, s), 4.20 (2H, q, J = 7.2 Hz).

(3) Pivaloyl chloride (0.51 g, 4.23 mmol) was added to a solution of 2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetic acid (2 g, 3.85 mmol) and triethylamine (0.41 g, 4.04 mmol) in acetonitrile (15 ml) at 0°C and the mixture was stirred at 0°C for 30 minutes. To the reaction solution was added ethyl 4-amino-3-oxobutanoate hydrochloride (0.84 g, 4.62 mmol) obtained in Examples 1-(2) at 0°C and then added dropwise a solution of triethylamine (0.58 g, 5.77 mmol) in acetonitrile (2 ml).

After stirring at room temperature for 30 minutes, the reaction solution was diluted with ethyl acetate (50 ml), washed with 0.1N hydrochloric acid, a 5% aqueous potassium hydrogen sulfate solution, an aqueous saturated sodium hydrogen carbonate solution and an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (1:3)] to obtain ethyl 4-({2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]acetyl}amino)-3-oxobutanoate (1.8 g, 2.75 mmol, 71%) as colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.01 (3H, s), 1.28 (3H, t, J = 7.0 Hz), 2.03 (3H, s), 2.71 (1H, dd, J = 5.6, 14.8

Hz), 2.79 (1H, dd, J = 7.4, 14.8 Hz), 3.48 (2H, s), 3.54 (1H, d, J = 14.2 Hz), 3.62 (3H, s), 3.71 (1H, d, J = 11.4 Hz), 3.86 (1H, d, J = 11.4 Hz), 3.89 (3H, s), 4.14-4.25 (4H, m), 4.37 (1H, dd, J = 5.6, 7.4 Hz), 4.55 (1H, d, J = 14.2 Hz), 6.26 (1H, s), 6.58-6.62 (1H, br), 6.63 (1H, s), 6.96-7.33 (5H, m).

(4) A solution of ethyl 4-({2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]acetyl}amino)-3-oxobutanoate (0.5 g, 0.773 mmol) obtained in Example 1-(3) and a Lawesson's reagent (0.46 g, 1.16 mmol) in THF (5 ml) was stirred at 70°C for 1 hour. The reaction solution was concentrated under reduced pressure and the residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (1:1)] to obtain ethyl (2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetate (0.41 g, 0.635 mmol, 82%) as colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.03 (3H, s), 1.28 (3H, t, J = 7.2 Hz), 2.03 (3H, s), 3.44 (1H, dd, J = 7.2, 15.0 Hz), 3.55 (1H, dd, J = 6.9, 15.0 Hz), 3.58 (1H, d, J = 14.4 Hz), 3.62 (3H, s), 3.73 (1H, d, J = 10.8 Hz), 3.80 (2H, s), 3.85 (1H, d, J = 10.8 Hz), 3.89 (3H, s), 4.20 (2H, q, J =

7.2 Hz), 4.33 (1H, dd, J = 6.9, 7.2 Hz), 4.57 (1H, d, J = 14.4 Hz), 6.31 (1H, s), 6.60 (1H, t, J = 2.1 Hz), 6.96-7.34 (5H, m), 7.43 (1H, s).

(5) A mixture of ethyl (2-{[(3R, 5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetate (0.3 g, 0.465 mmol) obtained in Example 1-(4), a 1N aqueous sodium hydroxide solution (1 ml) and ethanol (3 ml) was stirred at 60°C for 30 minutes. This mixture was diluted with water (50 ml), acidified and then extracted with ethyl acetate (50 ml) twice. These extracts was washed with an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was recrystallized from ethanol-hexane (1:5) to obtain (2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetic acid (0.23 g, 0.400 mmol, 86%) as a colorless prismatic crystal.

m.p.: 219-222°C (dec.) (EtOH-hexane).

$[\alpha]_D^{22}$ -209.2° (c = 0.34, MeOH).

IR ν_{max}(KBr) cm^{-1}: 3500-2400, 1724, 1658.

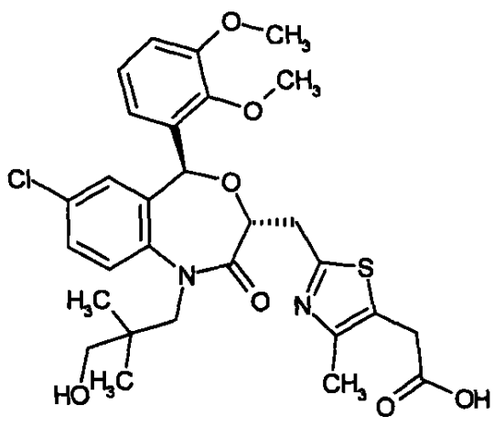
^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 3.19 (1H, d, J = 12.3 Hz), 3.38 (1H, d, J = 14.4 Hz), 3.46 (1H, dd, J = 7.2, 15.0 Hz), 3.59 (1H, dd, J = 6.0, 15.0 Hz), 3.61 (3H,

s), 3.64 (1H, d, J = 12.3 Hz), 3.82 (2H, s), 3.88 (3H, s), 4.35 (1H, dd, J = 6.0, 7.2 Hz), 4.47 (1H, d, J = 14.4 Hz), 6.20 (1H, s), 6.58 (1H, d, J = 1.8 Hz), 6.96-7.36 (5H, m), 7.48 (1H, s).

nal. Calcd for $C_{28}H_{31}N_2O_7ClS$: C, 58.48; H, 5.43; N, 4.87. Found: C, 58.32; H, 5.30; N, 4.68.

Example 2

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-4-methyl-1,3-thiazol-5-yl)acetic acid



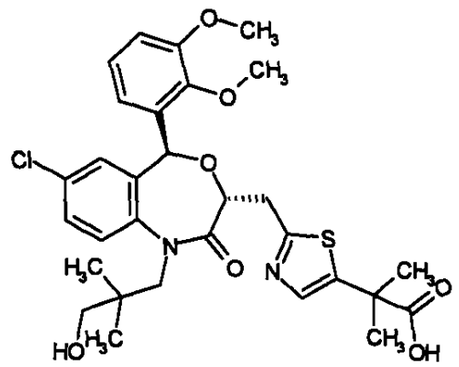
According to a similar manner to that of Example 1, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.641 (3H, s), 1.05 (3H, s), 2.29 (3H, s), 3.18 (1H, d, J = 12.3 Hz), 3.37 (1H, d, J = 13.8 Hz), 3.42 (1H, dd, J = 6.9, 15.0 Hz), 3.54 (1H, dd, J = 5.4, 15.0 Hz), 3.61 (3H, s), 3.64 (1H, d, J = 12.3 Hz), 3.73 (2H,

s), 3.88 (3H, s), 4.29 (1H, dd, J = 5.4, 6.9 Hz), 4.47 (1H, d, J = 13.8 Hz), 6.19 (1H, s), 6.57 (1H, d, J = 2.1 Hz), 6.96-7.35 (5H, m).

Example 3

2-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-2-methylpropionic acid

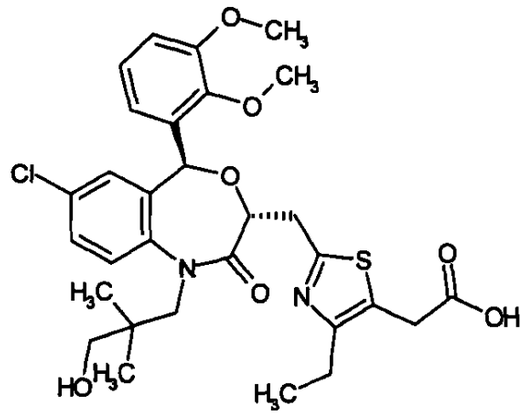


According to a similar manner to that of Example 1, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.67 (3H, s), 1.04 (3H, s), 1.65 (6H, s), 3.15 (1H, d, J = 11.6 Hz), 3.41 (1H, dd, J = 7.2, 14.8 Hz), 3.41 (1H, dd, J = 14.4 Hz), 3.54 (1H, dd, J = 6.2, 14.8 Hz), 3.61 (3H, s), 3.62 (1H, d, J = 11.6 Hz), 3.89 (3H, s), 4.34 (1H, dd, J = 6.2, 7.2Hz), 4.48 (1H, d, J = 14.4 Hz), 6.20 (1H, s), 6.55 (1H, s), 6.96-7.36 (5H, m), 7.46 (1H, s).

Example 4

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-4-ethyl-1,3-thiazol-5-yl)acetic acid



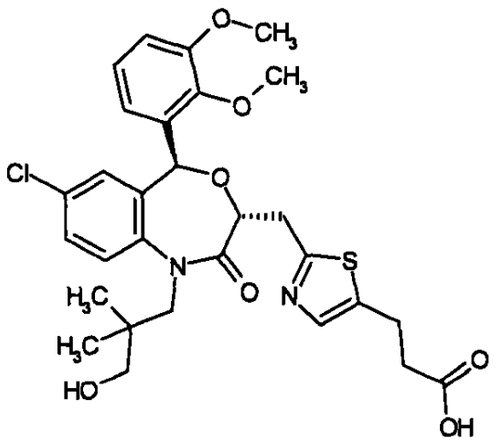
According to a similar manner to that of Example 1, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 1.18 (3H, t, J = 7.5 Hz), 2.63 (2H, q, J = 7.5 Hz), 3.18 (1H, d, J = 12.0 Hz), 3.37 (1H, d, J = 14.4 Hz), 3.43 (1H, dd, J = 7.2, 15.0 Hz), 3.54 (1H, dd, J = 6.0, 15.0 Hz), 3.61 (3H, s), 3.64 (1H, d, J = 12.0 Hz), 3.74 (2H, s), 3.88 (3H, s), 4.31 (1H, dd, J = 6.0, 7.2 Hz), 4.47 (1H, d, J = 14.4 Hz), 6.19 (1H, s), 6.57 (1H, d, J = 1.8Hz), 6.95-7.36 (5H, m).

Example 5

3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-

hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)propionic acid



(1) Carbonyldiimidazole (9.7 g, 60 mmol) was added to a solution of monoethylsuccinic acid (7.3 g, 50 mmol) in THF (70 ml) and the mixture was stirred at room temperature for 1 hour. To the reaction solution were added magnesium chloride (4.8 g, 50 mmol) and potassium monoethylmalonate (8.5 g, 50 mmol) and the mixture was stirred at 60°C for 1 hour. The mixture was filtered to remove insoluble substances and the filtrate was concentrated under reduced pressure. The residue was diluted with water, acidified and then extracted with ethyl acetate (70 ml) twice. The extracts were washed with an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (3:1)] to obtain diethyl 3-

oxohexanedioate (8.9 g, 41.2 mmol, 82%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J = 7.2 Hz), 1.29 (3H, t, J = 7.2 Hz), 2.61 (2H, t, J = 6.6 Hz), 2.87 (2H, t, J = 6.6 Hz), 3.50 (97/100 × 2H, s), 4.14 (2H, q, J = 7.2 Hz), 4.21 (2H, q, J = 7.2 Hz), 5.02 (3/100 × 1H, s).

(2) A solution of sodium nitrite (3.3 g, 48 mmol) in water (40 ml) was added dropwise to a solution of diethyl 3-oxohexanedioate (8.7 g, 40.2 mmol) obtained in Example 5-(1) in acetic acid (20 ml) under ice-cooling. Further, water (60 ml) was added and the mixture was stirred overnight. The reaction solution was extracted with ethyl acetate (50 ml) twice. The extracts were washed with an aqueous saturated sodium hydrogen carbonate solution and an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography [developing solution: hexane-ethyl acetate (2:1)] to obtain diethyl 2-hydroxyimino-3-oxohexanedioate (9.3 g, 37.9 mmol, 94%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J = 7.4 Hz), 1.35 (3H, t, J = 7.4 Hz), 2.68 (2H, t, J = 6.6 Hz), 3.17 (2H, t, J = 6.6 Hz), 4.17 (2H, q, J = 7.4 Hz), 4.38 (2H, q, J = 7.4 Hz).

(3) Zinc powder (18.7 g, 0.286 mol) was added to a solution of diethyl 2-hydroxyimino-3-oxohexanedioate (9 g, 36.7 mmol) obtained in Example 5-(2) and acetic anhydride

(26 g, 0.220 mol) in acetic acid (120 ml) at room temperature and the mixture was stirred for 24 hours. The mixture was filtered to remove insoluble substances and the insoluble substances were washed with ethyl acetate (50 ml). The filtrate and the washing solution were combined and then concentrated under reduced pressure to obtain diethyl 2-acetylamino-3-oxohexanedioate (9.0 g, 32.9 mmol, 90%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J = 7.2 Hz), 1.33 (3H, t, J = 7.2 Hz), 2.08 (3H, s), 2.62-2.67 (2H, m), 2.95 (1H, dt, J = 18.6, 6.6 Hz), 3.11 (1H, dt, J = 18.6, 6.6 Hz), 4.12 (2H, q, J = 7.2 Hz), 4.29 (2H, q, J = 7.2 Hz), 5.30 (1H, d, J = 6.6 Hz), 6.68 (1H, d, J = 6.6 Hz).

(4) Diethyl 2-acetylamino-3-oxohexanedioate (8.8 g, 32.2 mmol) obtained in Example 5-(3) was added to a 4N HCl solution in ethyl acetate (90 ml) and the mixture was heated to reflux for 4 hours. The reaction solution was concentrated under reduced pressure and the residue was crystallized from ethyl acetate-ether to obtain 5-amino-4-oxopentanoic acid hydrochloride (4.4 g, 26.3 mmol, 82%) as a colorless needle crystal.

^{1}H-NMR (CD_3OD) δ: 2.65 (2H, t, J = 7.0 Hz), 2.81 (2H, t, J = 7.0 Hz), 4.02 (2H, s).

(5) Pivaloyl chloride (0.51 g, 4.23 mmol) was added to a solution of 2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-

7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetic acid (2 g, 3.85 mmol) and triethylamine (0.41 g, 4.04 mmol) in acetonitrile (15 ml) at 0°C and the mixture was stirred at 0°C for 30 minutes. To the reaction solution at 0°C, 5-amino-4-oxopentanoic acid hydrochloride (0.77 g, 4.62 mmol) obtained in Example 5-(4) was added and a solution of triethylamine (0.58 g, 5.77 mmol) in acetonitrile (2 ml) was then added dropwise.

After stirring at room temperature for 30 minutes, the reaction solution was diluted with ethyl acetate (50 ml), washed with 0.1N hydrochloric acid and an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was dissolved in DMF (30 ml), potassium carbonate (0.65 g, 4.69 mmol) and methyl iodide (0.67 g, 4.69 mmol) were added, and the mixture was stirred at room temperature for 1 hour. The reaction solution was diluted with ethyl acetate (100 ml), washed with water, a 5% aqueous potassium hydrogen sulfate solution, an aqueous saturated sodium hydrogen carbonate solution and an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (1:3)] to obtain methyl 5-({2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-

dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]acetyl}amino)-4-oxopentanoate (1.2 g, 1.85 mmol, 44%) as colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.02 (3H, s), 2.03 (3H, s), 2.60-2.76 (5H, m), 2.93 (1H, dd, J = 7.0, 14.6 Hz), 3.53 (1H, d, J = 14.4 Hz), 3.61 (3H, s), 3.68 (3H, s), 3.71 (1H, d, J = 12.0 Hz), 3.86 (1H, d, J = 12.0 Hz), 3.89 (3H, s), 4.17 (2H, d, J = 4.6 Hz), 4.38 (1H, dd, J = 6.8, 7.0 Hz), 4.55 (1H, d, J = 14.4 Hz), 6.26 (1H, s), 6.58 (1H, t, J = 4.6 Hz), 6.63 (1H, s), 6.96-7.32 (5H, m).

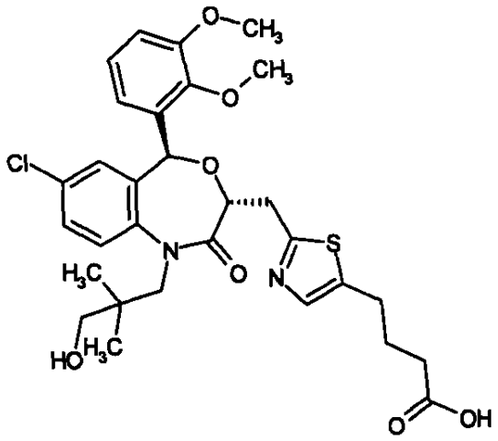
(6) According to the similar manners to those of Examples 1-(4) to (5), 3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)propionic acid was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.68 (2H, t, J = 7.0 Hz), 3.11 (2H, t, J = 7.0 Hz), 3.17 (1H, d, J = 11.8 Hz), 3.38 (1H, d, J = 14.2 Hz), 3.42 (1H, dd, J = 7.0, 15.4 Hz), 3.57 (1H, dd, J = 5.8, 15.4 Hz), 3.62 (3H, s), 3.64 (1H, d, J = 11.8 Hz), 3.89 (3H, s), 4.34 (1H, dd, J = 5.8, 7.0 Hz), 4.48 (1H, d, J = 14.2 Hz), 6.20 (1H, s), 6.58 (1H, s), 6.97-7.37 (6H, m).

Example 6

3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-

hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)butanoic acid

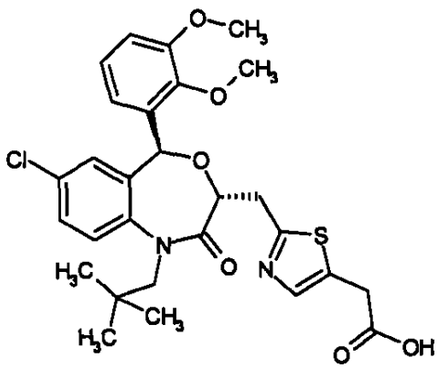


According to a similar manner to that of Example 5, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 1.96 (2H, quintet, J = 7.0 Hz), 2.41 (2H, t, J = 7.0 Hz), 2.86 (2H, t, J = 7.0 Hz), 3.17 (1H, d, J = 11.8 Hz), 3.38 (1H, d, J = 14.4 Hz), 3.43 (1H, dd, J = 7.0, 15.0 Hz), 3.57 (1H, dd, J = 5.8, 15.0 Hz), 3.62 (3H, s), 3.64 (1H, d, J = 11.8 Hz), 3.89 (3H, s), 4.35 (1H, dd, J = 5.8, 7.0 Hz), 4.48 (1H, d, J = 14.4 Hz), 6.20 (1H, s), 6.58 (1H, d, J = 1.8 Hz), 6.96-7.38 (6H, m).

Example 7

2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetic acid

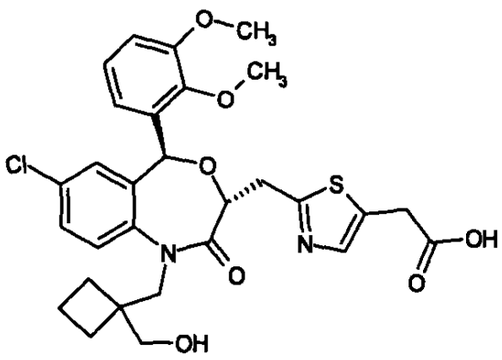


According to a similar manner to that of Example 1, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 3.34 (1H, d, J = 13.5 Hz), 3.46 (1H, dd, J = 7.2, 15.0 Hz), 3.57 (1H, dd, J = 6.0, 15.0 Hz), 3.62 (3H, s), 3.84 (2H, s), 3.88 (3H, s), 4.33 (1H, dd, J = 6.0, 7.2 Hz), 4.50 (1H, d, J = 13.5 Hz), 6.31 (1H, s), 6.56 (1H, d, J = 2.1 Hz), 6.90-7.00 (1H, m), 7.10-7.20 (2H, m), 7.26 (1H, d, J = 8.7 Hz), 7.30 (1H, d, J = 2.1, 8.7 Hz),7.47 (1H, s).

Example 8

{2-[((3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-{[1-(hydroxymethyl)cyclobutyl]methyl}-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)methyl]-1,3-thiazol-5-yl}acetic acid

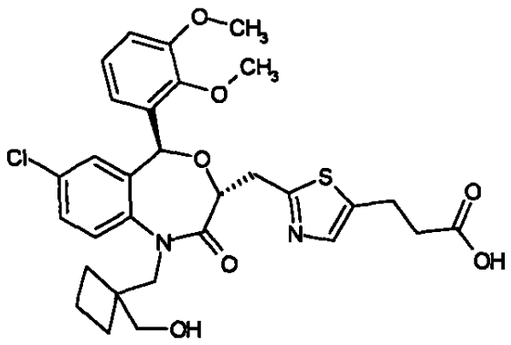


According to a similar manner to that of Example 1, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 1.33-1.55 (2H, m), 1.76-1.94 (3H, m), 1.96-2.12 (1H, m), 3.41-3.78 (9H, m), 3.83 (2H, s), 3.87 (3H, s), 4.34 (1H, dd, J = 6.0, 6.9 Hz), 4.58 (1H, d, J = 14.4 Hz), 6.08 (1H, s), 6.57 (1H, d, J = 2.1 Hz), 6.95 (1H, dd, J = 1.8, 7.8 Hz), 7.07-7.18 (2H, m), 7.33-7.42 (2H, m), 7.48 (1H, s).

Example 9

3-{2-[((3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-{[1-(hydroxymethyl)cyclobutyl]methyl}-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)methyl]-1,3-thiazol-5-yl}propionic acid

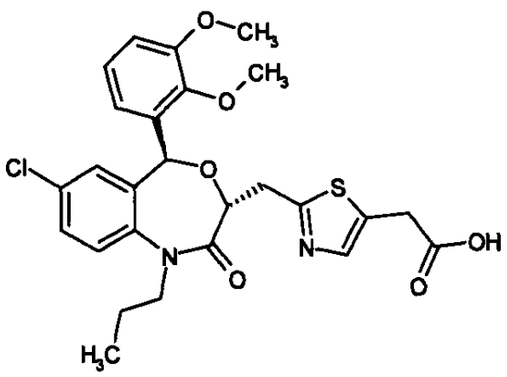


According to a similar manner to that of Example 5, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 1.34-1.55 (2H, m), 1.77-1.95 (3H, m), 1.98-2.10 (1H, m), 2.68 (2H, t, J = 7.5 Hz), 3.11 (2H, t, J = 7.5 Hz), 3.42 (1H, dd, J = 6.9, 15.0 Hz), 3.50-3.82 (7H, m), 3.89 (3H, s), 4.34 (1H, t, J = 6.41 Hz), 4.58 (1H, d, J = 14.32 Hz), 6.09 (1H, s), 6.58 (1H, d, J = 2.1 Hz), 6.98 (1H, dd, J = 1.8, 8.1 Hz), 7.09 (1H, dd, J = 1.5, 7.8 Hz), 7.17 (1H, t, J = 8.1 Hz), 7.35-7.43 (3H, m).

Example 10

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1-propyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetic acid

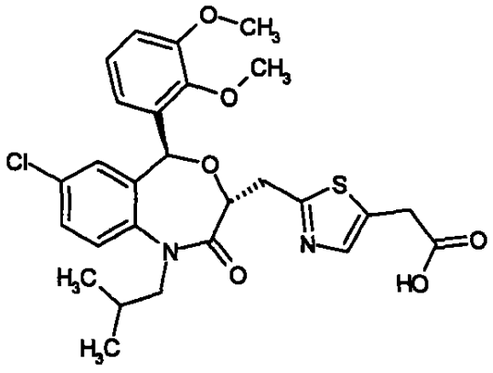


According to a similar manner to that of Example 1, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J = 7.5 Hz), 1.57-1.81 (2H, m), 3.43-3.63 (6H, m), 3.84 (2H, s), 3.87 (3H, s), 4.30-4.52 (2H, m), 6.11 (1H, s), 6.60 (1H, d, J = 1.8 Hz), 6.91-7.36 (5H, m), 7.49 (1H, s)

Example 11

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetic acid

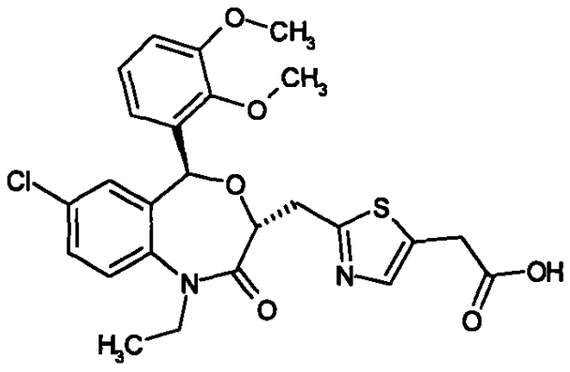


According to a similar manner to that of Example 1, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J = 6.4 Hz), 1.01 (3H, d, J = 6.8 Hz), 1.95-2.08 (1H, m), 3.32-3.62 (6H, m), 3.82 (2H, s), 3.87 (3H, s), 4.31-4.40 (2H, m), 6.21 (1H, s), 6.59 (1H, d, J = 2.3 Hz), 6.92-7.35 (5H, m), 7.49 (1H, s).

Example 12

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetic acid

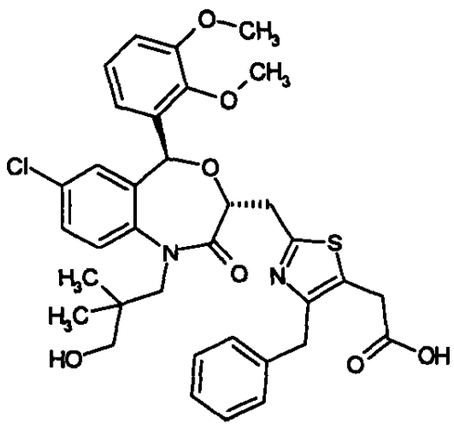


According to a similar manner to that of Example 1, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J = 7.2 Hz), 3.43-3.64 (6H, m), 3.84 (2H, s), 3.87 (3H, s), 4.33 (1H, t, J = 6.0 Hz), 4.49-4.62 (1H, m), 6.08 (1H, s), 6.60 (1H, d, J = 1.8 Hz), 6.91-7.36 (5H, m), 7.48 (1H, s).

Example 13

(4-Benzyl-2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetic acid



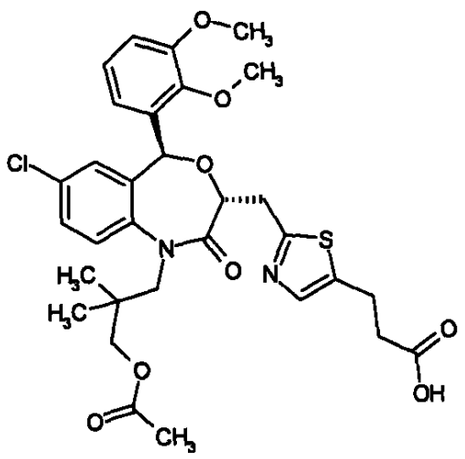
According to a similar manner to that of Example 1, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 3.15 (1H, d, J = 11.7 Hz), 3.32 (1H, d, J = 14.4 Hz), 3.41 (1H, dd, J = 7.5, 14.7 Hz), 3.53 (1H, dd, J = 6.3, 14.7 Hz), 3.60 (3H, s), 3.62 (1H, d, J = 11.7 Hz), 3.76 (2H, s), 3.87 (3H, s), 4.00 (2H, s), 4.32-4.38 (1H, m), 4.42 (1H, d, J = 14.4 Hz), 6.17 (1H, s), 6.55 (1H, d, J = 2.4 Hz), 6.95 (1H, dd, J = 2.1, 7.2 Hz), 7.02-7.30 (8H, m), 7.32 (1H, dd, J = 2.4, 8.7 Hz).

Example 14

3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-

(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)propionic acid



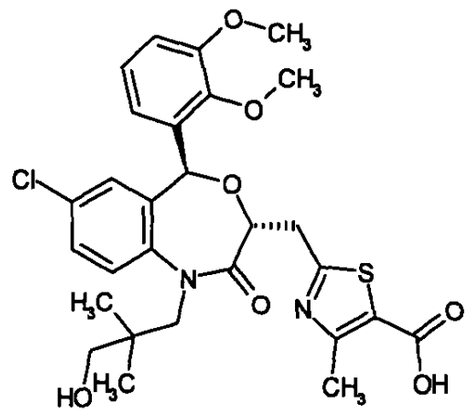
To a solution of 3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)propionic acid (0.5 g, 0.849 mmol) obtained in Example 5 in THF (10 ml), pyridine (0.34 ml, 4.24 mol) was added at room temperature and acetyl chloride (0.18 ml, 2.55 mmol) was then added dropwise. The mixture was stirred for 2.5 hours. After water (5 ml) was added, the mixture was stirred at room temperature for 19 hours and the reaction solution was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain 3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-

1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)propionic acid (0.5 g, 0.792 mmol, 93%) as colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.23 (3H, s), 2.02 (3H, s), 2.68 (2H, t, J = 7.5 Hz), 3.10 (2H, t, J = 7.5 Hz), 3.42 (1H, dd, J = 7.2, 15.0 Hz), 3.53 (1H, d, J = 14.1 Hz), 3.54 (1H, dd, J = 6.3, 15.0 Hz), 3.61 (3H, s), 3.73 (1H, d, J = 11.1 Hz), 3.85 (1H, d, J = 11.1 Hz), 3.88 (3H, s), 4.32 (1H, dd, J = 6.3, 7.2 Hz), 4.56 (1H, d, J = 14.1 Hz), 6.29 (1H, s), 6.59 (1H, d, J = 2.1 Hz), 6.96 (1H, dd, J = 2.1, 7.8 Hz), 7.06-7.26 (2H, m), 7.27 (1H, d, J = 8.7 Hz), 7.31 (1H, dd, J = 2.1, 8.7 Hz), 7.35 (1H, s).

Example 15

2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-4-methyl-1,3-thiazol-5-carboxylic acid



(1) DMF(0.01 ml) was added to a solution of 2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetic acid (3 g, 6.49 mmol) and thionyl chloride (2.3 g, 19.5 mmol) in THF (10 ml). The reaction solution was stirred at room temperature for 1 hour and then concentrated under reduced pressure. The residue was dissolved in THF (10 ml) and added dropwise to a solution of hydrogen sulfide in pyridine (30 ml). The reaction solution was stirred at 0°C for 1 hour and then diluted with 2.5M sulfuric acid. The product was extracted with ethyl acetate (50 ml), washed with an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure to obtain [(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]thio-S-acetic acid (6.53 g) as colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.02 (3H, s), 2.03 (3H, s), 3.11 (1H, dd, J = 6.2, 16.4 Hz), 3.33 (1H, dd, J = 7.0, 16.4 Hz), 3.54 (1H, d, J = 14.0 Hz), 3.61 (3H, s), 3.72 (1H, d, J = 11.4 Hz), 3.85 (1H, d, J = 11.4 Hz), 3.89 (3H, s), 4.37 (1H, dd, J = 6.2, 7.0 Hz), 4.56 (1H, d, J = 14.0 Hz), 6.25 (1H, s), 6.64 (1H, d, J = 1.8 Hz), 6.96-7.35 (5H, m).

(2) A solution of [(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-

tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]thio-S-acetic acid (1 g, 1.87 mmol) obtained in Example 15-(1), triethylamine (0.41 g, 4.04 mmol) and methyl 2-chloroacetoacetate (0.31 g, 2.06 mmol) in ether (10 ml) was heated to reflux for 2 hours. After water was added to the reaction solution, the mixture was extracted with ethyl acetate (50 ml), washed with an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (2:1)] to obtain methyl 2-({2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]acetyl}thio)-3-oxobutanoate (0.9 g, 1.38 mmol, 74%) as colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.02 (3H, s), 2.02 (3H, s), 2.18 (3H, s), 3.14-3.26 (2H, m), 3.53 (1H, d, J = 14.4 Hz), 3.61 (3H, s), 3.72 (1H, d, J = 12.0 Hz), 3.74 (9/10 × 3H, s), 3.78 (1/10 × 3H, s), 3.85 (1H, d, J = 12.0 Hz), 3.89 (3H, s), 4.43 (1H, t, J = 6.4 Hz), 4.54 (1H, d, J = 14.4 Hz), 5.50 (1/10 × 3H, s), 6.26 (1H, s), 6.62 (1H, d, J = 1.8 Hz), 6.96-7.35 (5H, m).

(3) A solution of methyl 2-({2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]acetyl}thio)-3-oxobutanoate (0.8 g, 1.23 mmol) obtained

in Example 15-(2) and ammonium acetate (0.33 g, 4.32 mmol) in acetic acid (5 ml) was heated to reflux for 1 hour. The reaction solution was diluted with ethyl acetate (50 ml), washed with an aqueous saturated sodium hydrogen carbonate solution and an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (3:2)]to obtain methyl 2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepın-3-yl]methyl}-4-methyl-1,3-thiazol-5-carboxylate (0.62 g, 0.982 mmol, 80%) as colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.03 (3H, s), 2.03 (3H, s), 2.65 (3H, s), 3.421 (1H, dd, J = 7.0, 14.8 Hz), 3.53 (1H, d, J = 14.0 Hz), 3.56 (1H, dd, J = 6.0, 14.8 Hz), 3.62 (3H, s), 3.72 (1H, d, J = 11.4 Hz), 3.86 (3H, s),3.86 (1H, d, J = 11.4 Hz), 3.89 (3H, s), 4.31 (1H, dd, J = 6.0, 7.0 Hz), 4.56 (1H, d, J = 14.0 Hz), 6.30 (1H, s), 6.61 (1H, d, J = 2.2 Hz), 6.96-7.37 (5H, m).

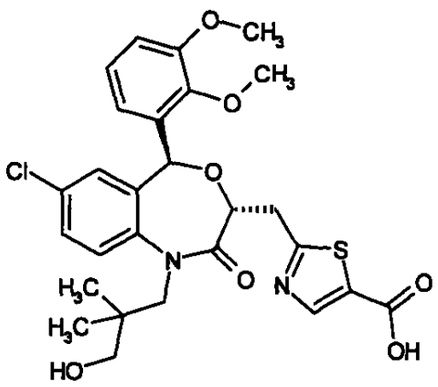
(4) A mixture of methyl 2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-4-methyl-1,3-thiazol-5-carboxylate (0.4 g, 0.634 mmol) obtained in Example 15-(3), a 1N aqueous sodium hydroxide solution (2

ml) and ethanol (4 ml) was stirred at 60°C for 30 minutes. This mixture was diluted with water (50 ml), acidified and then extracted with ethyl acetate (50 ml) twice. The extracts were washed with an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was recrystallized from ethanol-hexane (1:1) to obtain 2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-4-methyl-1,3-thiazol-5-carboxylic acid (0.15 g, 0.261 mmol, 41%) as a colorless prismatic crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s), 1.04 (3H, s), 2.65 (3H, s), 3.16 (1H, d, J = 12.0 Hz), 3.40 (1H, d, J = 14.1 Hz), 3.43 (1H, dd, J = 6.9, 14.4 Hz), 3.55 (1H, dd, J = 5.7, 14.1 Hz), 3.62 (1H, d, J = 12.0 Hz), 3.62 (3H, s), 3.90 (3H, s),4.32 (1H, dd, J = 5.7, 6.9 Hz), 4.47 (1H, d, J = 14.1 Hz), 6.21 (1H, s), 6.59 (1H, s), 6.99-7.38 (5H, m).

Example 16

2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-carboxylic acid



(1) To a solution of 2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetic acid (10 g, 19.2 mmol) in DMF (100 ml), 1-hydroxy-1H-benzotriazole ammonium salt (4.1 g, 26.9 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (5.16 g, 26.9 mmol) were added. After the mixture was stirred at room temperature for 13 hours, water (50 ml) was added and the mixture was diluted with ethyl acetate (350 ml). The organic layer was washed with 1N hydrochloric acid, aqueous saturated sodium hydrogen carbonate solution, water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain 3-[(3R,5S)-3-(2-amino-2-oxoethyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (10.0 g) as colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.01 (3H, s), 2.03 (3H,

s), 2.68 (1H, dd, J = 5.7, 14.7 Hz), 2.87 (1H, dd, J = 7.5, 14.7 Hz), 3.54 (1H, d, J = 13.8 Hz), 3.61 (3H, s), 3.73 (1H, d, J = 11.1 Hz), 3.86 (1H, d, J = 11.1 Hz), 3.89 (3H, s), 4.39 (1H, dd, J = 5.7, 7.5 Hz), 4.56 (1H, d, J = 13.8 Hz), 5.46 (1H, br), 5.95 (1H, br), 6.26 (1H, s), 6.64 (1H, d, J = 2.4 Hz), 6.91-7.01 (1H, m), 7.15-7.24 (2H, m), 7.31 (1H, d, J = 8.4 Hz), 7.35 (1H, dd, J = 2.4, 8.4 Hz).

(2) A solution of 3-[(3R,5S)-3-(2-amino-2-oxoethyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (10.8 g, 20.8 mmol) obtained in Example 16-(1) and a Lawesson's reagent (10.1 g, 24.8 mmol) in THF (100 ml) was heated to reflux for 1 hour with stirring. After standing to cool to room temperature, an aqueous saturated sodium hydrogen carbonate solution (20 ml) was added and the mixture was stirred for 30 minutes. The reaction solution was extracted with ethyl acetate (800 ml), washed with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (1:1)] to obtain 3-[(3R,5S)-3-(2-amino-2-thioxoethyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (5.14 g) as a white crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.01 (3H, s), 2.03 (3H, s), 3.08 (1H, dd, J = 5.4, 13.5 Hz), 3.31 (1H, dd, J = 7.5, 13.5 Hz), 3.55 (1H, d, J = 14.1 Hz), 3.55 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.72 (1H, d, J = 11.4 Hz), 3.86 (1H, d, J = 11.4 Hz), 3.89 (3H, s), 4.46 (1H, dd, J = 5.4, 7.5 Hz), 4.53 (1H, d, J = 14.1 Hz), 6.26 (1H, s), 6.65 (1H, d, J = 2.4 Hz), 6.91-7.01 (1H, m), 7.15-7.24 (2H, m), 7.31 (1H, d, J = 8.7 Hz), 7.36 (1H, dd, J = 2.4, 8.7 Hz), 7.49 (1H, br), 7.64 (1H, br)

(3) Acetic acid (0.13 ml, 2.34 mmol) was added to a suspension of ethyl 2-chloro-3-oxopropionate potassium salt (0.42 g, 2.24 mmol) in isopropanol (10 ml) and the mixture was stirred for 30 minutes. Thereto 3-[(3R,5S)-3-(2-amino-2-thioxoethyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (1.0 g, 1.87 mmol) obtained in Example 16-(2) was added and the mixture was heated to reflux for 30 hours with stirring. After standing to cool, water (5 ml) was added to the reaction solution, followed by extraction with ethyl acetate (200 ml). The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (7:3-65:35)] to obtain ethyl 2-{[(3R, 5S)-1-[3-

acetoxy-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-caboxylate (0.6 g) as colorless noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 1.31 (3H, t, J = 7.2 Hz), 2.03 (3H, s), 2.82 (1H, dd, J = 5.7, 16.8 Hz), 2.92 (1H, dd, J = 7.5, 16.8 Hz), 3.54 (1H, d, J = 14.1 Hz), 3.62 (3H, s), 3.72 (1H, d, J = 11.1 Hz), 3.85 (1H, d, J = 11.1 Hz), 3.87 (3H, s), 4.12 (2H, q, J = 7.2 Hz), 4.19 (1H, dd, J = 5.7, 7.5 Hz), 4.57 (1H, d, J = 14.1 Hz), 6.28 (1H, s), 6.53-6.55 (1H, m), 6.89-7.40 (5H, m), 8.70 (1H, s).

(4) Potassium carbonate (0.26 g, 1.91 mmol) was added to a solution of ethyl 2-{[(3R,5S)-1-[3-acetoxy-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-caboxylate (0.6 g, 0.95 mmol) obtained in Example 16-(3) in methanol (6 ml) and the mixture was stirred at room temperature for 2 hours. Water (3 ml) was added to the reaction solution, followed by extraction with ethyl acetate (80 ml). The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (67:33-3:2)] to obtain methyl 2-{[(3R,5S)-7-chloro-

5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl-1,3-thiazol-5-carboxylate (0.3 g) as colorless noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 3.07-3.21 (1H, m), 3.38 (1H, d, J = 14.1 Hz), 3.58-3.70 (1H, m), 3.61 (3H, s), 3.73 (2H, d, J = 6.6 Hz), 3.85 (3H, s), 3.88 (3H, s), 4.48 (1H, d, J = 14.1 Hz), 4.53 (1H, t, J = 6.6 Hz), 6.17 (1H, s), 6.52-6.55 (1H, m), 6.90-7.10 (2H, m), 7.07-7.20 (1H, m), 7.26-7.40 (2H, m), 8.71 (1H, s).

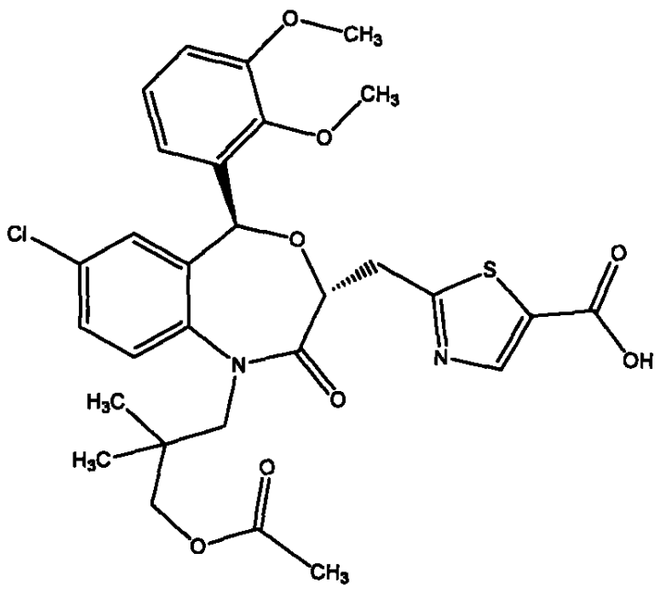
(5) A mixture of methyl 2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl-1,3-thiazol-5-carboxylate (0.3 g, 0.52 mmol) obtained in Example 16-(4), 1N aqueous sodium hydroxide solution (1 ml) and ethanol (5 ml) was stirred at room temperature for 8 hours. After this mixture was acidified with 1N hydrochloric acid (1.2 ml), ethyl acetate (70 ml) was added thereto. The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting crystal was washed with hexane to obtain 2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-carboxylic acid

(0.19 g) as a white crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s), 1.05 (3H, s), 3.19 (1H, d, J = 12.3 Hz), 3.40 (1H, d, J = 14.1 Hz), 3.58-3.78 (3H, m), 3.61 (3H, s), 3.87 (3H, s), 4.47 (1H, d, J = 14.1 Hz), 4.57 (1H, t, J = 6.0 Hz), 6.18 (1H, s), 6.56 (1H, s), 6.90-7.01 (2H, m), 7.12 (1H, t, J = 7.8 Hz), 7.30-7.40 (2H, m), 8.76 (1H, s).

Example 17

2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-carboxylic acid



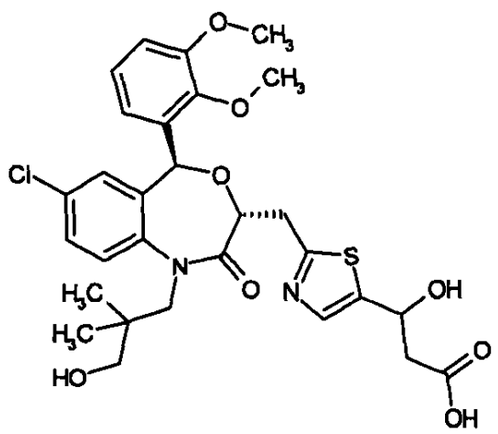
After pyridine (0.9 ml, 8.91 mol) was added to a solution of 2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-

4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-acetic acid (1.0 g, 1.78 mmol) obtained in Example 16 in THF(10 ml) at room temperature, acetyl chloride (0.38 ml, 5.35 mmol) was added dropwise and the mixture was stirred for 1 hour. Thereto pyridine (0.3 ml, 3.71 mmol) and then acetyl chloride (0.1 ml, 1.41 mmol) were added and the mixture was further stirred for 30 minutes. After water (5 ml) was added, the mixture was stirred at room temperature for 19 hours and the reaction solution was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain 2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-carboxylic acid (0.76 g) as pale brown noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 2.03 (3H, s), 3.42-3.63 (3H, m), 3.63 (3H, s), 3.73 (1H, d, J = 11.1 Hz), 3.70-3.90 (1H, m), 3.85 (1H, d, J = 11.1 Hz), 3.89 (3H, s), 4.55 (1H, d, J = 14.1 Hz), 4.50-4.60 (1H, m), 6.29 (1H, s), 6.63 (1H, d, J = 2.7 Hz), 6.98 (1H, dd, J = 1.5, 8.1 Hz), 7.08 (1H, dd, J = 1.5, 8.1 Hz), 7.17 (1H, t, J = 8.1 Hz), 7.29 (1H, d, J = 9.0 Hz), 7.34 (1H, dd, J = 2.7, 9.0 Hz), 8.76 (1H, s).

Example 18

3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-hydroxypropionic acid



(1) 1,1'-Carbonyldiimidazole (0.24 g, 1.49 mol) was added to a solution of 2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-carboxylic acid (0.75 g, 1.24 mmol) obtained in Example 17 in THF (10 ml) at room temperature and the mixture was stirred for 1 hour. Monoethyl malonate potassium (0.23 g, 1.37 mmol) and magnesium chloride (0.13 g, 1.37 mmol) were added and the mixture was stirred at 55°C for 1 hour. After standing to cool, 1N hydrochloric acid (3 ml) was added and the mixture was extracted with

ethyl acetate (150 ml). The organic layer was washed with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (67:33-1:1)] to obtain ethyl 3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-oxopropionate (0.59 g, 0.88 mmol, 71%) as colorless noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.03 (3H, s), 1.26 (3H, t, J = 7.5 Hz), 2.03 (3H, s), 3.54 (1H, d, J = 14.1 Hz), 3.58-3.80 (2H, m), 3.60 (3H, s), 3.73 (1H, d, J = 10.8 Hz), 3.84 (1H, d, J = 10.8 Hz), 3.87 (3H, s), 3.93 (1H, d, J = 15.9 Hz), 4.00 (1H, d, J = 15.9 Hz), 4.12 (2H, q, J = 7.5 Hz), 4.50 (1H, t, J = 6.6 Hz), 4.54 (1H, d, J = 14.1 Hz), 6.28 (1H, s), 6.56 (1H, s), 6.89-7.00 (2H, m), 7.10 (1H, t, J = 7.8 Hz), 7.30-7.34 (2H, m), 8.74 (1H, s).

(2) A suspension of ethyl 3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-oxopropionate (0.59 g, 0.88 mmol) obtained in Example 18-(1) in ethanol (20 ml) was cooled to -20°C and sodium borohydride (36 mg, 0.96 mmol) was added thereto. After stirring for 2 hours, an aqueous saturated ammonium

chloride solution (5 ml) was added and the mixture was extracted with ethyl acetate (150 ml). The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (55:45-35:65)] to obtain ethyl 3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-hydroxypropionate (0.49 g) as colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, s), 0.97 (3H, s), 1.26 (3H, t, J = 7.2 Hz), 2.04 (3H, s), 2.77 (1H, dd, J = 5.1, 15.9 Hz), 2.94 (1H, dd, J = 9.0, 15.9 Hz), 3.05-3.21 (2H, m), 3.42 (1H, d, J = 14.1 Hz), 3.62 (3H, s), 3.66 (1H, d, J = 11.7 Hz), 3.82 (1H, d, J = 11.7 Hz), 3.89 (3H, s), 4.12 (2H, q, J = 7.2 Hz), 4.42 (1H, d, J = 14.1 Hz), 4.30-4.52 (1H, m), 4.62-4.71 (1H, m), 5.62-5.80 (1H, m), 6.26 (1H, s), 6.62 (1H, d, J = 2.1 Hz), 6.98 (1H, dd, J = 2.4, 7.2 Hz), 7.10-7.26 (3H, m), 7.30 (1H, dd, J = 2.1, 8.7 Hz), 8.55 (1H, s).

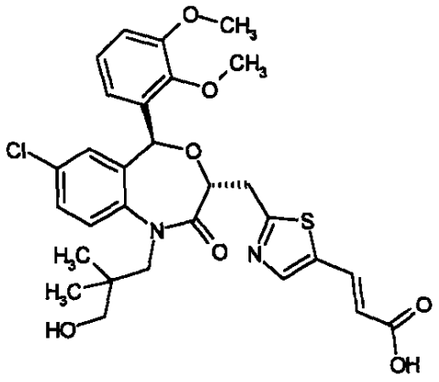
(3) A mixture of ethyl 3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-

thiazol-5-yl)-3-hydroxypropionate (0.06 g, 0.09 mmol) obtained in Example 18-(2), a 1N aqueous sodium hydroxide solution (0.5 ml) and ethanol (1 ml) was stirred at room temperature for 2 hours. This mixture was acidified with 1N hydrochloric acid (0.6 ml) and ethyl acetate (40 ml) was added thereto. The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting crystal was washed with hexane to obtain 3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-hydroxypropionic acid (0.05 g) as a white crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s), 1.00 (3H, s), 2.73 (1H, dd, J = 5.1, 16.2 Hz), 2.81 (1H, dd, J = 8.4, 16.2 Hz), 3.14 (1H, d, J = 12.0 Hz), 3.19 (1H, dd, J = 5.4, 14.1 Hz), 3.36 (1H, d, J = 14.1 Hz), 3.48 (1H, dd, J = 7.8, 14.1 Hz), 3.60 (1H, d, J = 12.0 Hz), 3.61 (3H, s), 3.89 (3H, s), 4.41 (1H, d, J = 14.1 Hz), 4.50 (1H, dd, J = 5.4, 7.8 Hz), 5.64 (1H, dd, J = 5.1, 8.4 Hz), 6.18 (1H, s), 6.56 (1H, d, J = 2.1 Hz), 6.95-7.03 (2H, m), 7.16 (1H, t, J = 7.8 Hz), 7.29 (1H, d, J = 9.0 Hz), 7.35 (1H, dd, J = 2.1, 9.0 Hz), 8.59 (1H, s).

Example 19

(2E)-3-(2-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acrylic acid



(1) Triethylamine (0.11 ml, 0.77 mmol) and methanesulfonyl chloride (0.05 ml, 0.68 mmol) were added to a solution of ethyl 3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-hydroxypropionate (0.4 g, 0.59 mmol) obtained in Example 18-(2) in THF (5 ml) under ice-cooling and the mixture was stirred for 1 hour. Triethylamine (0.11 ml, 0.77 mmol) and methanesulfonyl chloride (0.05 ml, 0.68 mmol) were additionally added thereto and the mixture was stirred for 1 hour. Then, DBU (0.12 ml, 0.77 mmol) was added thereto and the mixture was stirred for 1 hour. Then, water (10 ml) was added thereto and the mixture was extracted with ethyl acetate (150 ml). The organic layer was washed with water and an aqueous saturated sodium

chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (63:37-52:48)] to obtain ethyl (2E)-3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acrylate (0.05 g) as colorless noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, s), 1.05 (3H, s), 1.25 (3H, t, J = 7.2 Hz), 2.04 (3H, s), 3.40 (2H, d, J = 6.0 Hz), 3.54 (1H, d, J = 14.0 Hz), 3.61 (3H, s), 3.73 (1H, d, J = 11.0 Hz), 3.86 (1H, d, J = 11.0 Hz), 3.87 (3H, s), 4.19 (2H, q, J = 7.2 Hz), 4.37 (1H, t, J = 6.6 Hz), 4.57 (1H, d, J = 14.0 Hz), 6.18 (1H, d, J = 15.4 Hz), 6.28 (1H, s), 6.54 (1H, s), 6.88 (1H, dd, J = 1.4, 7.6 Hz), 6.92 (1H, dd, J = 1.4, 7.6 Hz), 7.05 (1H, t, J = 7.6 Hz), 7.23-7.38 (2H, m), 7.92 (1H, d, J = 15.4 Hz), 8.63 (1H, s).

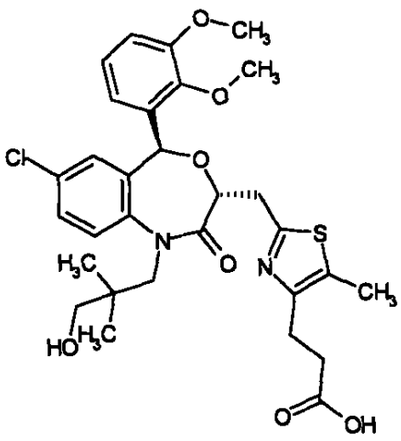
(2) A mixture of ethyl (2E)-3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acrylate (0.34 g, 0.52 mmol) obtained in Example 19-(1), a 1N aqueous sodium hydroxide solution (1.5 ml) and ethanol (7 ml) was stirred at 40°C for 1 hour. After standing to cool, this mixture was

acidified with 1N hydrochloric acid (1.7 ml) and ethyl acetate (160 ml) was added. The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting crystal was washed with hexane to obtain (2E)-3-(2-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acrylic acid (0.28 g) as a pale yellow crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.06 (3H, s), 3.19 (1H, d, J = 11.7 Hz), 3.37 (1H, d, J = 13.8 Hz), 3.39-3.45 (2H, m), 3.61 (3H, s), 3.67 (1H, d, J = 11.7 Hz), 3.86 (3H, s), 4.38 (1H, t, J = 7.2 Hz), 4.46 (1H, t, J = 13.8 Hz), 6.16 (1H, d, J = 15.6 Hz), 6.16 (1H, s), 6.53 (1H, d, J = 2.1 Hz), 6.88 (1H, dd, J = 1.5, 8.1 Hz), 6.93 (1H, dd, J = 1.5, 8.1 Hz), 7.08 (1H, t, J = 8.1 Hz), 7.29 (1H, d, J = 8.7 Hz), 7.33 (1H, dd, J = 2.1, 8.7 Hz), 8.02 (1H, d, J = 15.6 Hz), 8.66 (1H, s).

Example 20

3- (2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-5-methyl-1,3-thiazol-4-yl)propionic acid



(1) Pivaloyl chloride (0.51 g, 4.23 mmol) was added to a solution of 2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetic acid (2 g, 3.85 mmol) and triethylamine (0.41 g, 4.04 mmol) in acetonitrile (15 ml) at 0°C and the mixture was stirred at 0°C for 30 minutes. To the reaction solution at 0°C, methyl (4S)-4-amino-5-oxohexanoate hydrochloride (0.83 g, 4.24 mmol) was added and a solution of triethylamine (0.58 g, 5.77 mmol) in acetonitrile (2 ml) was then added dropwise.

After stirring at room temperature for 30 minutes, the reaction solution was diluted with ethyl acetate (50 ml), washed with 0.1N hydrochloric acid, a 5% aqueous potassium hydrogen sulfate solution, an aqueous saturated sodium hydrogen carbonate solution and an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was

purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (1:2)] to obtain methyl (4S)-4-({2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]acetyl}amino)-5-oxohexanoate (1.85 g, 2.80 mmol, 73%) as colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.02 (3H, s), 1.78-1.90 (1H, m), 2.03 (3H, s), 2.23 (3H, s), 2.25-2.42 (3H, m), 2.70 (1H, dd, J = 5.4, 14.4 Hz), 2.89 (1H, dd, J = 7.8, 14.4 Hz), 3.54 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.67 (3H, s), 3.72 (1H, d, J = 11.1 Hz), 3.85 (1H, d, J = 11.1 Hz), 3.89 (3H, s), 4.36 (1H, dd, J = 5.4, 7.8 Hz), 4.54 (1H, d, J = 14.1 Hz), 4.56-4.65 (1H, m), 6.25 (1H, s), 6.60-6.64 (1H, br), 6.64 (1H, s), 6.97-7.32 (5H, m).

(2) A solution of methyl (4S)-4-({2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]acetyl}amino)-5-oxohexanoate (0.51 g, 0.773 mol) obtained in Example 20-(1) and Lawesson's reagent (0.40 g, 1.00 mmol) in THF (5 ml) was stirred at 70°C for 1 hour. The reaction solution was concentrated under reduced pressure and the residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (1:1)] to obtain methyl 3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-

tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]methyl}-5-methyl-1,3-thiazol-4-yl)propionate (0.31 g, 0.470 mmol, 61%) as colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.03 (3H, s), 2.03 (3H, s), 2.34 (3H, s), 2.64 (2H, t, J = 7.4 Hz), 2.87(2H, t, J = 7.4 Hz), 3.34 (1H, dd, J = 6.8, 15.0 Hz), 3.50 (1H, dd, J = 6.2, 15.0 Hz), 3.53 (1H, d, J = 14.2 Hz), 3.62 (3H, s), 3.63 (3H, s), 3.72 (1H, d, J = 11.0 Hz), 3.85 (1H, d, J = 11.0 Hz), 3.89 (3H, s), 4.27 (1H, dd, J = 6.2, 6.8 Hz), 4.56 (1H, d, J = 14.2 Hz), 6.29 (1H, s), 6.60 (1H, d, J = 1.8 Hz), 6.95-7.36 (5H, m).

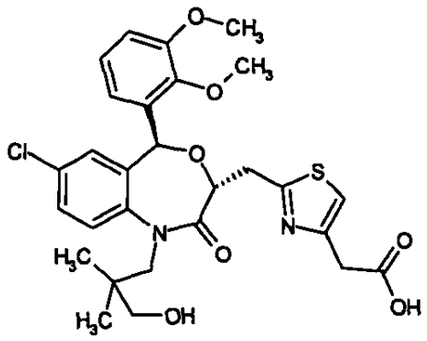
(3) A mixture of methyl 3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]methyl}-5-methyl-1,3-thiazol-4-yl)propionate (0.2 g, 0.303 mmol) obtained in Example 20-(2), a 1N aqueous sodium hydroxide solution (1 ml) and ethanol (2 ml) was stirred at 60°C for 30 minutes. This mixture was diluted with water (50 ml), acidified, and extracted with ethyl acetate (50 ml) twice. This extract was washed with an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure to obtain 3-((2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-5-methyl-1,3-thiazol-4-

yl)propionic acid (0.18 g, 0.298 mmol, 98%) as colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.33 (3H, s), 2.66-2.72 (2H, m), 2.83-2.89 (2H, m), 3.16 (1H, d, J = 11.8 Hz), 3.37 (1H, dd, J = 6.2, 15.4 Hz), 3.42 (1H, d, J = 14.6 Hz), 3.59 (1H, dd, J = 6.6, 15.4 Hz), 3.62 (3H, s), 3.63 (1H, d, J = 11.8 Hz), 3.90 (3H, s), 4.30 (1H, dd, J = 6.2, 6.6 Hz), 4.46 (1H, d, J = 14.6 Hz), 6.20 (1H, s), 6.60 (1H, d, J = 1.4 Hz), 6.97-7.39 (5H, m).

Example 21

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-4-yl)acetic acid



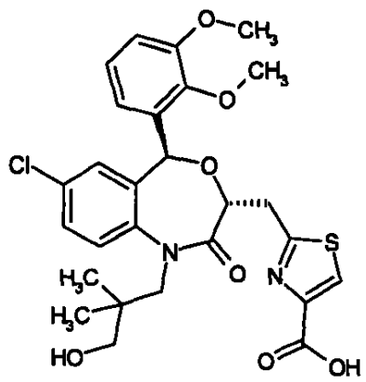
According to a similar manner to that of Example 16, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 3.17 (1H, d, J = 11.9 Hz), 3.41 (1H, d, J = 14.5 Hz), 3.48 (1H, dd, J = 6.5, 15.4 Hz), 3.60-3.71 (5H, m), 3.80 (2H, s), 3.90 (3H,

s), 4.35 (1H, t, J = 6.5 Hz), 4.46 (1H, d, J = 14.5 Hz), 6.21 (1H, s), 6.60 (1H, s), 7.00 (1H, dd, J = 2.1, 7.7 Hz), 7.05 (1H, s), 7.11-7.22 (2H, m), 7.33-7.40 (2H, m).

Example 22

2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-4-carboxylic acid



(1) A solution of 3-[(3R,5S)-3-(2-amino-2-oxoethyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (3.0 g, 5.61 mmol) obtained in Example 16-(2) and ethyl 3-bromo-2-oxopropionate (0.79 ml, 6.28 mmol) in ethanol (30 ml) was heated to reflux for 2 hours with stirring. After standing to stand, water (15 ml) was added to the reaction solution, followed by extraction with ethyl acetate (300 ml). The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then

concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (3:2-1:1)] to obtain ethyl 2-{[(3R,5S)-1-[3-acetoxy-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-4-carboxylate (1.1 g) as colorless noncrystalline powder from a first eluted fraction, and ethyl 2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-4-carboxylate (2.0 g) as colorless powder from a second eluted fraction.

First eluted fraction

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.03 (3H, s), 1.37 (3H, t, J = 7.0 Hz), 2.03 (3H, s), 3.41-3.62 (3H, m), 3.61 (3H, s), 3.72 (1H, d, J = 11.0 Hz), 3.96 (1H, d, J = 11.0 Hz), 3.89 (3H, s), 4.27-4.40 (1H, m), 4.39 (2H, q, J = 7.0 Hz), 4.55 (1H, d, J = 14.0 Hz), 6.31 (1H, s), 6.59 (1H, d, J = 1.8 Hz), 6.98 (1H, dd, J = 2.0, 7.8 Hz), 7.08 (1H, dd, J = 2.0, 7.8 Hz), 7.17 (1H, t, J = 7.8 Hz), 7.23-7.40 (2H, m), 8.09 (1H, s).

Second eluted fraction

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 1.38 (3H, t, J = 7.0 Hz), 3.16 (1H, t, J = 11.8 Hz), 3.37 (1H, d, J = 14.4 Hz), 3.45-3.72 (3H, m), 3.62 (3H, s), 3.89 (3H, s),

4.05-4.15 (1H, m), 4.35 (1H, t, J = 7.0 Hz), 4.39 (2H, q, J = 7.0 Hz), 4.47 (1H, d, J = 14.4 Hz), 6.21 (1H, s), 6.56 (1H, d, J = 2.2 Hz), 6.99 (1H, dd, J = 1.8, 8.0 Hz), 7.07 (1H, dd, J = 1.8, 8.0 Hz), 7.18 (1H, t, J = 8.0 Hz), 7.29 (1H, d, J = 8.4 Hz), 7.35 (1H, dd, J = 2.2, 8.4 Hz), 8.09 (1H, s).

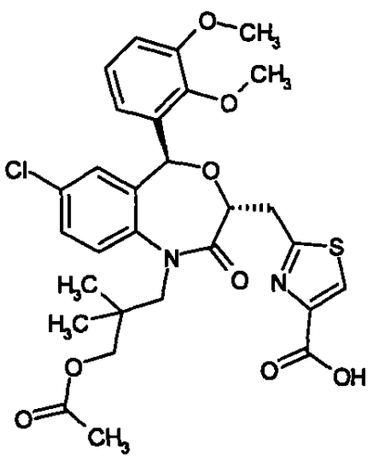
(2) A mixture of ethyl 2-{[(3R,5S)-1-[3-acetoxy-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-4-carboxylate (0.34 g, 0.52 mmol) and ethyl 2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-4-carboxylate (2.0 g, 3.40 mmol) obtained in Example 22-(1), a 1N aqueous sodium hydroxide solution (14.0 ml) and ethanol (60 ml) was stirred at room temperature for 5 hours. This mixture was acidified with 1N hydrochloric acid (14.5 ml) and ethyl acetate (380 ml) was added thereto. The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. To the resulting residue were added diethyl ether (30 ml), a 1N aqueous sodium hydroxide solution (14 ml) and water (100m). The aqueous layer was washed with diethyl ether (50 ml) and then acidified with 1N hydrochloric acid (14.5 ml) and ethyl acetate (380 ml)

was added thereto. The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain 2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-4-carboxylic acid (2.9 g) as pale yellow noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 3.18 (1H, d, J = 12.0 Hz), 3.38 (1H, d, J = 13.8 Hz), 3.54 (1H, dd, J = 7.2, 14.7 Hz), 3.56-3.68 (1H, m), 3.62 (3H, s), 3.89 (3H, s), 4.34 (1H, dd, J = 5.7, 7.2 Hz), 4.46 (1H, d, J = 13.8 Hz), 6.21 (1H, s), 6.57 (1H, d, J = 2.1 Hz), 6.98 (1H, dd, J = 1.5, 8.1 Hz), 7.06 (1H, dd, J = 1.5, 8.1 Hz), 7.17 (1H, t, J = 8.1 Hz), 7.29 (1H, d, J = 8.7 Hz), 7.35 (1H, dd, J = 2.1, 8.7 Hz), 8.18 (1H, s).

Example 23

2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-4-carboxylic acid

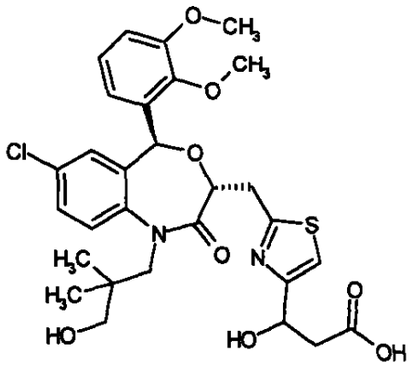


According to a similar manner to that of Example 17, the title was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.03 (3H, s), 2.03 (3H, s), 3.45-3.66 (3H, m), 3.61 (3H, s), 3.72 (1H, d, J = 10.8 Hz), 3.85 (1H, d, J = 10.8 Hz), 3.89 (3H, s), 4.32 (1H, dd, J = 5.7, 7.2 Hz), 4.55 (1H, d, J = 13.8 Hz), 6.31 (1H, s), 6.60 (1H, d, J = 2.4 Hz), 6.98 (1H, dd, J = 1.5, 7.8 Hz), 7.06 (1H, dd, J = 1.5, 7.8 Hz), 7.10-7.20 (1H, m), 7.27 (1H, d, J = 9.0 Hz), 7.32 (1H, dd, J = 2.4, 9.0 Hz), 8.18 (1H, s).

Example 24

3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-4-yl)-3-hydroxypropionic acid

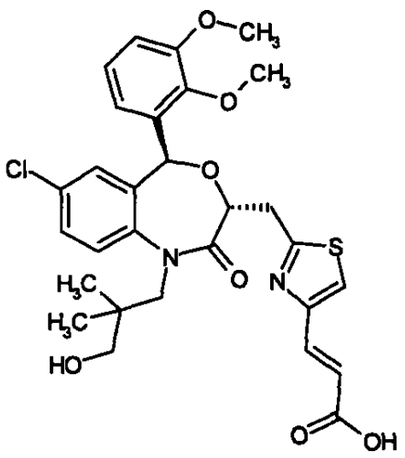


According to a similar manner to that of Example 18, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 2.78-3.04 (2H, m), 3.16 (1H, d, J = 11.4 Hz), 3.39 (1H, d, J = 14.1 Hz), 3.40-3.70 (3H, m), 3.61 (3H, s), 3.89 (3H, s), 4.31 (1H, t, J = 6.6 Hz), 4.46 (1H, d, J = 14.1 Hz), 5.11-5.21 (1H, m), 6.20 (1H, s), 6.59 (1H, s), 6.96-7.02 (1H, m), 7.08-7.20 (3H, m), 7.29-7.41 (2H, m)

Example 25

(2E)-3-{2-[((3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)methyl]-1,3-thiazol-4-yl}acrylic acid

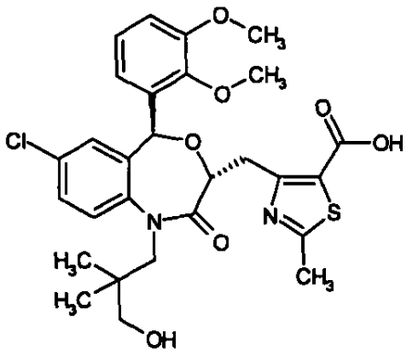


According to a similar manner to that of Example 19, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s), 1.06 (3H, s), 3.18 (1H, d, J = 12.0 Hz), 3.41 (1H, d, J = 13.8 Hz), 3.49 (1H, dd, J = 6.6, 15.3 Hz), 3.58-3.70 (2H, m), 3.63 (3H, s), 3.90 (3H, s), 4.40 (1H, t, J = 6.6 Hz), 4.48 (1H, d, J = 13.8 Hz), 6.23 (1H, s), 6.60 (1H, d, J = 2.4 Hz), 6.62 (1H, d, J = 15.3 Hz), 7.00 (1H, dd, J = 2.4, 7.2 Hz), 7.13-7.21 (2H, m), 7.30-7.41 (3H, m), 7.62 (1H, d, J = 15.3 Hz).

Example 26

4-[((3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)methyl]-2-methyl-1,3-thiazol-5-carboxylic acid



(1) Carbonyldiimizazole (3.7 g) was added to a suspension of 2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetic acid (10 g) in THF (100 ml) and the mixture was stirred at room temperature for 2 hours. To the reaction solution were added magnesium chloride (2.2 g) and potassium monoethylmalonate (4.0 g) and the mixture was stirred at 60°C for 1 hour. The reaction solution was diluted with ethyl acetate (200 ml), washed with 1N hydrochloric acid, an aqueous saturated sodium hydrogen carbonate solution and an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain ethyl 4-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyhphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]}-3-oxobutanoate (10.2 g) as a white crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.01 (3H, s), 1.27 (3H,

s), 2.02 (3H, s), 2.96 (1H, dd, J = 5.0, 17.2 Hz), 3.27 (1H, dd, J = 7.8, 17.0 Hz), 3.42-3.57 (3H, m), 3.61 (3H, s), 3.69-3.82 (2H, m), 3.89 (3H, s), 4.18 (2H, q, J = 7.4 Hz), 4.41-4.57 (2H, m), 6.24 (1H, s), 6.63 (1H, s), 6.95-7.02 (1H, m), 7.15-7.20 (2H, m), 7.33-7.34 (4H, m)

(2) Sulfuryl chloride (0.23 ml) was added to a solution of ethyl 4-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]}-3-oxobutanoate (1.5 g) obtained in Example 26-(1) in dichloromethane (30 ml) and the mixture was stirred at room temperature for 2 hours. The reaction solution was poured into water, which was extracted with chloroform. The organic layer was concentrated under reduced pressure. Thioacetamide (0.21 g) and ethanol (30 ml) were added to the residue and the mixture was refluxed overnight. The reaction solution was concentrated and the residue was purified by silica gel column chromatography to obtain ethyl 4-[((3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)methyl]-2-methyl-1,3-thiazol-5-carboxylate (0.80 g) as a colorless amorphous crystal.

^{1}H-NMR (CD_3OD) δ: 0.93 (3H, s), 1.23 (3H, s), 1.27 (3H, t, J = 7.2 Hz), 2.03 (3H, s), 2.64 (3H, s), 3.51-3.57 (1H, m), 3.60 (3H, s), 3.67-3.85 (4H, m), 3.87 (3H, s), 4.23 (2H,

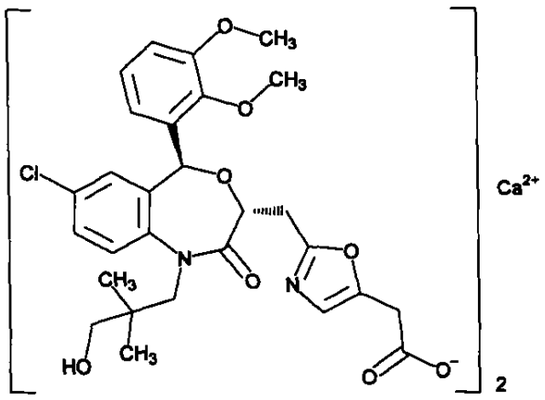
q, J = 7.2 Hz), 4.37-4.44 (2H, m), 6.26 (1H, s), 6.53 (1H, s), 6.87-6.99 (2H, m), 7.05-7.10 (1H, m), 7.16-7.18 (1H, m), 7.32-7.37(2H, m).

(3) A mixture of ethyl 4-[((3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)methyl]-2-methyl-1,3-thiazol-5-carboxylate (0.7 g) obtained in Example 26-(2), a 2N aqueous sodium hydroxide solution (2 ml) and ethanol (10 ml) was stirred at room temperature for 30 minutes. This mixture was diluted with water (50 ml), acidified, and extracted with chloroform (50 ml) twice. These extracts were washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain 4-[((3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)methyl]-2-methyl-1,3-thiazol-5-carboxylic acid (0.19 g) as a white crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.04 (3H, s), 1.12 (3H, s), 1.14 (3H, s), 2.62 (3H, s), 3.12-3.16 (1H, m), 3.35-3.40 (1H, m), 3.53 (3H, s), 3.62-3.68 (3H, m), 3.87 (3H, s), 4.41-4.50 (2H, m), 6.16 (1H, s), 6.53 (1H, s), 6.93-6.97 (2H, m), 7.09-7.14 (1H, m), 7.26-7.33(2H, m)

Example 27

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)acetic acid calcium salt



(1) Phosphorus oxychloride (0.35 g, 2.33 mmol) was added to a solution of ethyl 4-({2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]acetyl}amino)-3-oxobutanoate (1 g, 1.55 mmol) obtained in Example 1-(3) in DMF (3 ml) and the mixture was stirred at 70°C for 1 hour. The reaction solution was cooled in an ice bath and an aqueous saturated sodium hydrogen carbonate solution (50 ml) was added thereto. The product was extracted with ethyl acetate (50 ml) twice, washed with water and an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel

column chromatography [developing solvent: hexane-ethyl acetate (3:2)] to obtain ethyl (2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)acetate (0.57 g, 0.906 mmol, 58%) as colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.03 (3H, s), 1.26 (3H, t, J = 7.4 Hz), 2.03 (3H, s), 3.24 (1H, dd, J = 7.4, 15.8 Hz), 3.36 (1H, dd, J = 6.6, 15.8 Hz), 3.54 (1H, d, J = 14.0 Hz), 3.61 (3H, s), 3.68 (2H, s), 3.73 (1H, d, J = 11.4 Hz), 3.85 (1H, d, J = 11.4 Hz), 3.89 (3H, s), 4.18 (2H, q, J = 7.4 Hz), 4.44 (1H, dd, J = 6.6, 7.4 Hz), 4.58 (1H, d, J = 14.0 Hz), 6.30 (1H, s), 6.60 (1H, s), 6.85 (1H, s), 6.94-7.33 (5H, m).

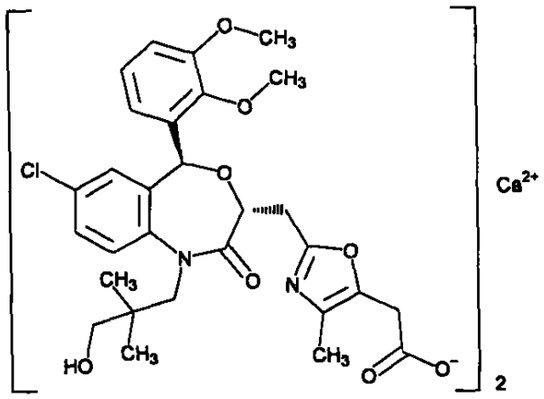
(2) A mixture of ethyl (2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)acetate (0.47 g, 0.747 mmol) obtained in Example 27-(1), a 1N aqueous sodium hydroxide solution (2 mmol) and ethanol (5 ml) was stirred at 60°C for 30 minutes. This mixture was washed with water (5 ml), acidified, and extracted with ethyl acetate (50 ml) twice. These extracts were washed with an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure to obtain (2-{[(3R,5S)-1-(3-acetoxy-

2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)acetic acid (0.42 g). This was dissolved in ethanol (6 ml) and a 1N aqueous sodium hydroxide solution (0.75 ml) was added thereto. The mixture was then concentrated under reduced pressure. The residue was dissolved in water (2 ml) and a solution of calcium chloride (42 mg, 0.378 mmol) in water (0.5 ml) was added. The produced precipitates were filtered to obtain (2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)acetic acid calcium salt (0.29 g, 0.247 mmol, 66%) as colorless powder.

^{1}H-NMR ($CDCl_3$-D_3OD (1:2)) δ: 0.81 (3H, s), 0.97 (3H, s), 3.19 (1H, d, J = 11.8 Hz), 3.22-3.29 (2H, m), 3.50 (1H, d, J = 11.8 Hz), 3.55 (2H, s), 3.60 (3H, s), 3.62 (1H, d, J = 13.4 Hz), 3.90 (3H, s), 4.40-4.47 (2H, m), 6.21 (1H, s), 6.55 (1H, d, J = 2.6 Hz), 6.78 (1H, s), 7.02-7.37 (5H, m).

Example 28

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-4-methyl-1,3-oxazol-5-yl)acetic acid calcium salt

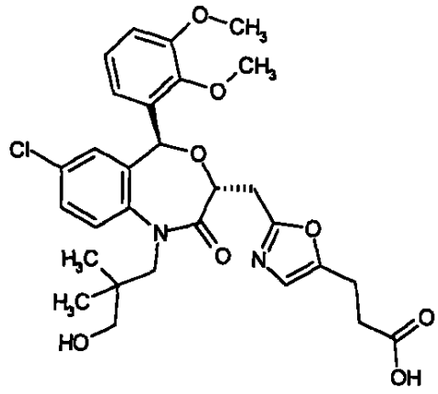


According to a similar manner to that of Example 27, the title compound was obtained.

^{1}H-NMR ($CDCl_3$-CD_3OD (1:2)) δ: 0.83 (3H, s), 0.95 (3H, s), 2.05 (3H, s), 3.18-3.26 (3H, m), 3.44-3.68 (4H, m), 3.59 (3H, s), 3.89 (3H, s), 4.38-4.46 (2H, m), 6.20 (1H, s), 6.53 (1H, d, J = 2.2 Hz), 7.02-7.59 (5H, m).

Example 29

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)propionic acid



(1) According to a similar manner to that of Example 27-(1), methyl (2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)propionate was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.03 (3H, s), 2.03 (3H, s), 2.64 (2H, t, J = 7.4 Hz), 2.96 (2H, t, J = 7.4 Hz), 3.21 (1H, dd, J = 7.0, 15.4 Hz), 3.33 (1H, dd, J = 6.6, 15.4 Hz), 3.54 (1H, d, J = 14.2 Hz), 3.61 (3H, s), 3.69 (3H, s), 3.73 (1H, d, J = 11.0 Hz), 3.85 (1H, d, J = 11.0 Hz), 3.89 (3H, s), 4.41 (1H, dd, J = 6.6, 7.0 Hz), 4.58 (1H, d, J = 14.2 Hz), 6.30 (1H, s), 6.60 (1H, s), 6.65 (1H, s), 6.95-7.33 (5H, m).

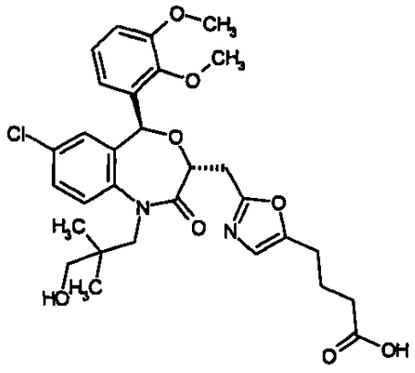
(2) A mixture of methyl (2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)propionate (0.11 g, 0.175 mmol) obtained in Example 29-(1), a 1N aqueous sodium hydroxide solution (0.5 ml) and ethanol (2 ml) was stirred at 60°C for 30 minutes. This was diluted with water (50 ml), acidified, and then extracted with ethyl acetate (50 ml) twice. This was washed with an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by recrystallization from ethanol-hexane (1:1) to obtain (2-

{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)propionic acid (50 mg, 0.0873 mmol, 50%) as colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 2.67 (2H, t, J = 7.0 Hz), 2.95 (2H, t, J = 7.0 Hz), 3.16 (1H, d, J = 12.8 Hz), 3.22 (1H, dd, J = 7.0, 15.8 Hz), 3.37 (1H, dd, J = 6.6, 15.8 Hz), 3.39 (1H, d, J = 15.4 Hz), 3.62 (3H, s), 3.63 (1H, d, J = 12.8 Hz), 3.89 (3H, s), 4.44 (1H, dd, J = 6.6, 7.0 Hz), 4.48 (1H, d, J = 15.4 Hz), 6.19 (1H, s), 6.59 (1H, s), 6.68 (1H, s), 6.96-7.36 (5H, m)

Example 30

4-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)butanoic acid



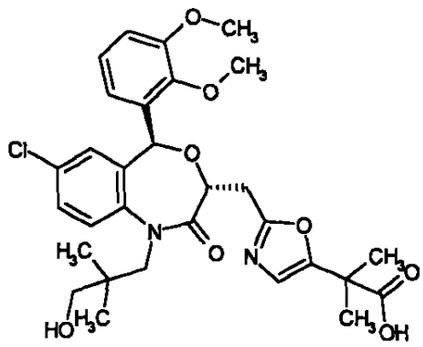
According to a similar manner to that of Example 29, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.04 (3H, s), 1.95 (2H,

quintet, J = 7.4 Hz), 2.38 (2H, t, J = 7.4 Hz), 2.69 (2H, t, J = 7.4 Hz), 3.16 (1H, d, J = 12.2 Hz), 3.21 (1H, dd, J = 6.6, 15.6 Hz), 3.38 (1H, dd, J = 7.0, 15.6 Hz), 3.40 (1H, d, J = 15.0 Hz), 3.61 (3H, s), 3.63 (1H, d, J = 12.2 Hz), 3.89 (3H, s), 4.42-4.52 (2H, m), 6.19 (1H, s), 6.58 (1H, s), 6.66 (1H, s), 6.95-7.36 (5H, m).

Example 31

2-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)-2-methylpropionic acid



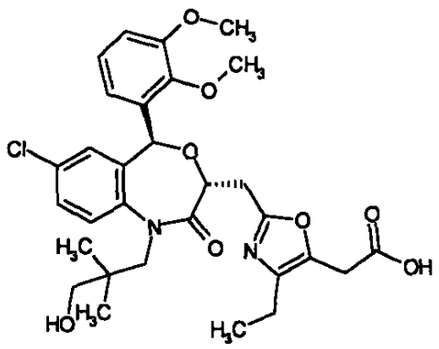
According to a similar manner to that of Example 29, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.037 (3H, s), 1.56 (6H, s), 3.17 (1H, d, J = 11.6 Hz), 3.25 (1H, dd, J = 7.0, 15.8 Hz), 3.38 (3H, dd, J = 6.6, 15.8 Hz), 3.39 (1H, d, J = 14.0 Hz), 3.61 (3H, s), 3.62 (1H, d, J = 11.6 Hz), 3.88 (3H, s), 4.41 (1H, dd, J = 6.6, 7.0 Hz), 4.47 (1H, d, J = 14.0

Hz), 6.18 (1H, s), 6.57 (1H, s), 6.80 (1H, s), 6.95-7.53 (5H, m).

Example 32

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-4-ethyl-1,3-oxazol-5-yl)acetic acid



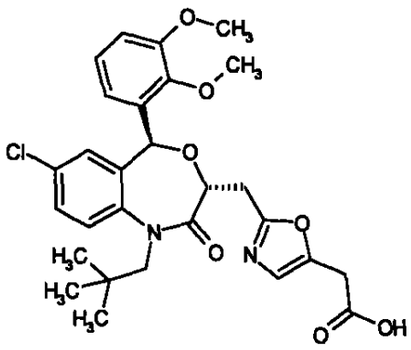
According to a similar manner to that of Example 29, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.04 (3H, s), 1.16 (3H, t, J = 7.6 Hz), 2.43 (2H, q, J = 7.6 Hz), 3.17 (1H, d, J = 12.0 Hz), 3.26-3.30 (2H, m), 3.38 (1H, d, J = 14.4 Hz), 3.60 (3H, s), 3.62 (2H, s), 3.62 (1H, d, J = 12.0 Hz), 3.87 (3H, s), 4.39-4.50 (2H, m), 6.17 (1H, s), 6.57 (1H, d, J = 1.4 Hz), 6.93-7.39 (5H, m).

Example 33

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-

2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)acetic acid

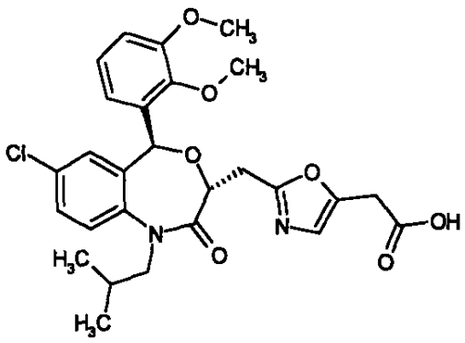


According to a similar manner to that of Example 29, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (9H, s), 3.27 (1H, dd, J = 7.2, 15.6 Hz), 3.35 (1H, dd, J = 6.0, 15.6 Hz), 3.36 (1H, d, J = 13.8 Hz), 3.61 (3H, s), 3.71 (2H, s), 3.87 (3H, s), 4.44 (1H, dd, J = 6.0, 7.2 Hz), 4.50 (1H, d, J = 13.8 Hz), 6.29 (1H, s), 6.56 (1H, s), 6.88 (1H, s), 6.94 (1H, dd, J = 1.5, 7.8 Hz), 7.03 (1H, dd, J = 0.9, 7.8 Hz), 7.13 (1H, t, J = 7.8 Hz), 7.26-7.34 (2H, m).

Example 34

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)acetic acid

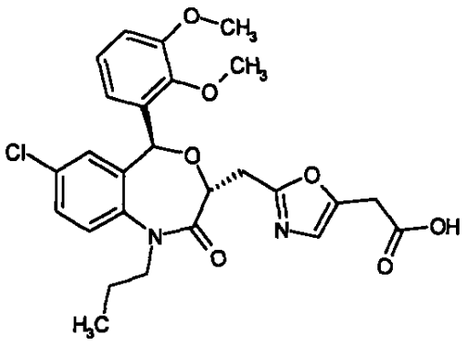


According to a similar manner to that of Example 29, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J = 6.6 Hz), 1.00 (3H, d, J = 6.9 Hz), 1.95-2.09 (1H, m), 3.32-3.41 (3H, m), 3.57 (3H, s), 3.69 (2H, s), 3.87 (3H, s), 4.37 (1H, t, J = 7.8, 13.8 Hz), 4.46 (1H, t, J = 6.3 Hz), 6.19 (1H, s), 6.60 (1H, d, J = 1.8 Hz), 6.90 (1H, s), 6.92-7.36 (5H, m).

Example 35

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1-propyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)acetic acid



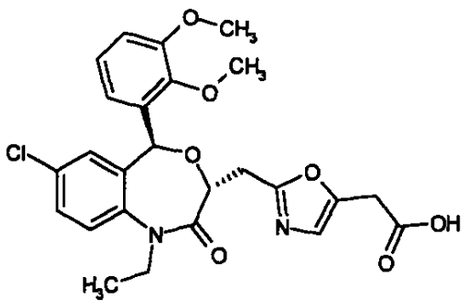
According to a similar manner to that of Example 29,

the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J = 7.5 Hz), 1.56-1.84 (2H, m), 3.23-3.54 (3H, m), 3.56 (3H, s), 3.69 (2H, s), 3.86 (3H, s), 4.40-4.52 (2H, m), 6.09 (1H, s), 6.60 (1H, d, J = 2.1 Hz), 6.90 (1H, s), 6.93-7.37 (5H, m).

Example 36

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)acetic acid



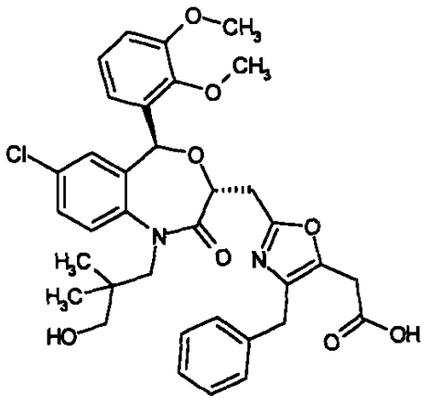
According to a similar manner to that of Example 29, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J = 7.2 Hz), 3.28 (1H, dd, J = 7.2, 15.6 Hz), 3.39 (1H, dd, J = 7.2, 15.6 Hz), 3.50-3.66 (4H, m), 3.69 (2H, s), 3.86 (3H, s), 4.45 (1H, t, J = 6.3 Hz), 4.48-4.62 (1H, m), 6.06 (1H, s), 6.61 (1H, d, J = 1.8 Hz), 6.90 (1H, s), 6.92-7.37 (5H, m).

Example 37

(4-Benzyl-2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-

(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)acetic acid



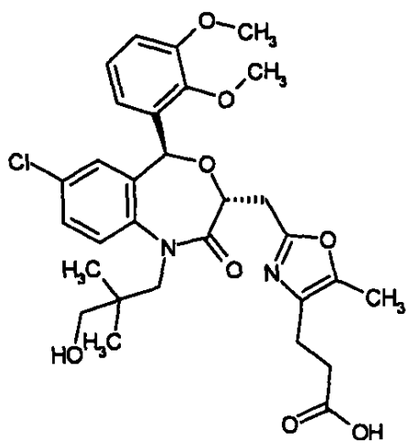
According to a similar manner to that of Example 29, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 3.15 (1H, d, J = 12.6 Hz), 3.26 (2H, dd, J = 4.5, 7.2 Hz), 3.35 (1H, d, J = 14.4 Hz), 3.51 (2H, d, J = 1.8 Hz), 3.59 (3H, s), 3.60 (1H, d, J = 12.6 Hz), 3.79 (2H, s), 3.86 (3H, s), 4.41 (1H, t, J = 7.2 Hz), 4.43 (1H, d, J = 14.4 Hz), 6.15 (1H, s), 6.55 (1H, d, J = 2.1 Hz), 6.93 (1H, dd, J = 1.5, 8.1 Hz), 6.98 (1H, dd, J = 1.5, 8.1 Hz), 7.08 (1H, t, J = 8.1 Hz), 7.13-7.26 (5H, m), 7.28 (1H, d, J = 9.0 Hz), 7.34 (1H, dd, J = 2.1, 9.0 Hz).

Example 38

3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-5-methyl-1,3-oxazol-4-

yl)propionic acid



(1) Phosphorus oxychloride (0.35 g, 2.33 mmol) was added to a solution of methyl (4S)-4-({2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]acetyl}amino)-5-oxohexanoate (1 g, 1.55 mmol) obtained in Example 20-(1) in DMF (3 ml) and the mixture was stirred at 80°C for 1 hour. The reaction solution was cooled in an ice bath and an aqueous saturated sodium hydrogen carbonate solution (50 ml) was added. The product was extracted with ethyl acetate (50 ml) twice, washed with water and an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography [developing solvent : hexane-ethyl acetate (1:1)] to obtain methyl 3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-

tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]methyl}-5-methyl-1,3-oxazol-4-yl)propionate (0.83 g, 1.29 mmol, 83%) as colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.03 (3H, s), 2.03 (3H, s), 2.22 (3H, s), 2.57-2.62 (2H, m), 2.66-2.71 (2H, m), 3.19 (1H, dd, J = 7.2, 15.6 Hz), 3.25 (1H, dd, J = 6.0, 15.6 Hz), 3.54 (1H, d, J = 13.8 Hz), 3.61 (3H, s), 3.64 (3H, s), 3.74 (1H, d, J = 11.1 Hz), 3.84 (1H, d, J = 11.1 Hz), 3.89 (3H, s), 4.36 (1H, dd, J = 6.0, 7.2 Hz), 4.57 (1H, d, J = 13.8 Hz), 6.29 (1H, s), 6.59 (1H, d, J = 1.8 Hz), 6.95-7.34 (5H, m).

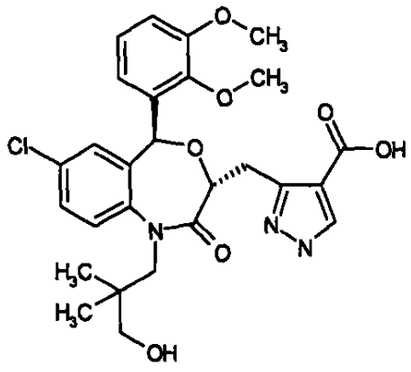
(2) A mixture of methyl 3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]methyl}-5-methyl-1,3-oxazol-4-yl)propionate (0.67 g, 1.04 mmol) obtained in Example 38-(1), a 1N aqueous sodium hydroxide solution (2.5 ml) and ethanol (7 ml) was stirred at 60°C for 30 minutes. This mixture was diluted with water (50 ml), acidified, and then extracted with ethyl acetate (50 ml) twice. The extract was washed with an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure to obtain 3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-5-methyl-1,3-oxazol-4-

yl)propionic acid (0.47 g, 0.801 mmol, 77%) as colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.22 (3H, s), 2.62-2.72 (4H, m), 3.12-3.19 (2H, m), 3.67-3.46 (2H, m), 3.62 (3H, s), 3.63 (1H, d, J = 12.3 Hz), 3.89 (3H, s), 4.39-4.48 (2H, m), 6.19 (1H, s), 6.60 (1H, d, J = 2.1 Hz), 6.98-7.47 (5H, m).

Example 39

3-[((3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)methyl]pyrazol-4-carboxylic acid



(1) N,N-dimethylformaldehydedimethylacetal (0.41 ml) was added to a solution of ethyl 4-[((3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)]-3-oxobutanoate (1.5 g) obtained in Example 26-(1) in toluene (30 ml) and the mixture was refluxed overnight. After the reaction

solution was concentrated, ethanol (30 ml) and hydrazine hydrate (0.14 g) were added to the residue and the mixture was refluxed for 3 hours. The reaction solution was concentrated and the residue was purified by silica gel column chromatography to obtain ethyl 3-[((3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-acetoxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)methyl]pyrazol-4-carboxylate (0.90 g) as a brown oil.

^{1}H-NMR (CD_3OD) δ: 0.95 (3H, s), 1.02 (3H, s), 1.26 (3H, t, J = 7.4 Hz), 2.03 (3H, s), 3.47-3.55 (2H, m), 3.62 (3H, s), 3.71-3.88 (2H, m), 3.89 (3H, s), 4.08-4.15 (2H, m), 4.21 (2H, q, J = 7.4 Hz), 4.54 (1H, d, J = 14.1 Hz), 6.27 (1H, s), 6.61 (1H, s), 6.96-6.99 (1H, m), 7.10-7.33 (4H, m), 7.87(1H, s).

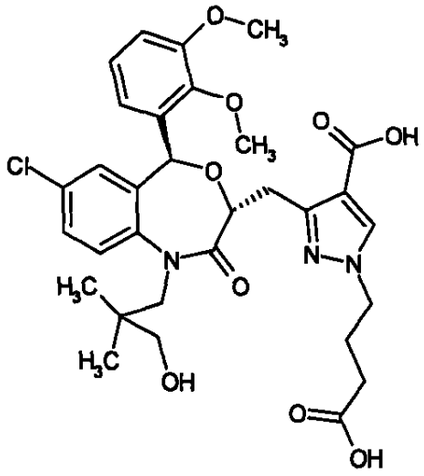
(2) A mixture of ethyl 3-[((3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)] methyl]pyrazol-4-carboxylate (1.0 g) obtained in Example 39-(1), a 2N aqueous saturated sodium hydroxide solution (3.3 ml) and ethanol (20 ml) was stirred at 80°C overnight. This mixture was diluted with water (50 ml), acidified, and then extracted with chloroform (50 ml) twice. This extract was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel

column chromatography to obtain 3-[((3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)methyl]pyrazol-4-carboxylic acid (0.18 g) as a white crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.06 (3H, s), 3.18 (1H, d, J = 11.7 Hz), 3.37 (1H, d, J = 15.0 Hz), 3.56-3.61 (3H, m), 3.63 (3H, s), 3.89 (3H, s), 4.14 (1H, t, J = 6.9 Hz), 4.49 (1H, d, J = 14.4 Hz), 6.19 (1H, s), 6.60 (1H, d, J = 2.4 Hz), 6.97-7.00 (1H, m), 7.08-7.10 (1H, m), 7.16-7.36 (5H, m), 7.94 (1H, s).

Example 40

1-(3-carboxypropyl)-3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1H-pyrazol-4-carboxylic acid



(1) Potassium carbonate (0.741 g) was added to a solution of ethyl-5-{[(3R,5S)-1-(3-(acetoxy)-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1H-pyrazol-4-carboxylate (3.00 g) obtained in Example 39-(1) and ethyl 4-bromobutanoate (0.794 ml) in DMF (30 ml) and the mixture was stirred overnight. The reaction solution was diluted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain ethyl 3-{[(3R,5S)-1-(3-(acetoxy)-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1-(4-ethoxy-4-oxobutyl)-1H-pyrazol-4-carboxylate (0.98 g) from a first eluted fraction and ethyl 5-({(3R,5S)-1-[3-(acetoxy)-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl}methyl)-1-(4-ethoxy-4-oxobutyl)-1H-pyrazol-4-carboxylate (1.78 g) from a second eluted fraction.

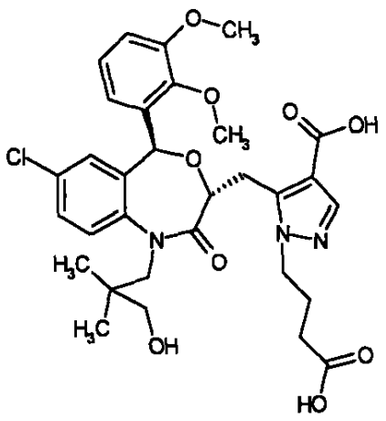
(2) To a solution of ethyl 3-{[(3R,5S)-1-(3-(acetoxy)-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1-(4-ethoxy-4-oxobutyl)-1H-pyrazol-4-carboxylate (0.8 g) obtained in Example 40-(1) in ethanol (8 ml) was added a 1N

aqueous sodium hydroxide solution (4 ml) and the mixture was stirred overnight. The reaction solution was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. This extract was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (157 mg).

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.03 (3H, s), 2.10-2.21 (2H, m), 2.28-2.38 (2H, m), 3.16 (1H, d, J = 12.1 Hz), 3.28-3.45 (2H, m), 3.52-3.69 (5H, m), 3.86 (3H, s), 4.13 (2H, t, J = 6.22 Hz), 4.41-4.52 (2H, m), 6.17 (1H, s), 6.56 (1H, d, J = 2.07 Hz), 6.94 (1H, dd, J = 1.9, 7.9 Hz), 7.05-7.17 (2H, m), 7.30-7.40 (2H, m), 7.85 (1H, s).

Example 41

1-(3-carboxypropyl)-5-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1H-pyrazol-4-carboxylic acid



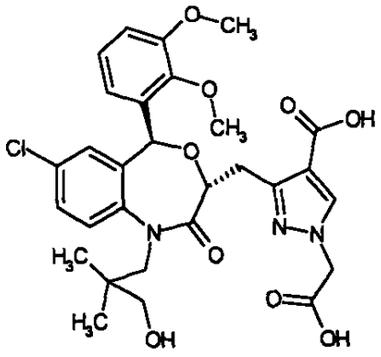
A 1N aqueous sodium hydroxide solution (4 ml) was added to a solution of ethyl 5-({(3R,5S)-1-[3-(acetyloxy)-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl}methyl)-1-(4-ethoxy-4-oxobutyl)-1H-pyrazol-4-carboxylate (0.75 g) obtained in Example 40-(1) in ethanol (20 ml) and the mixture was stirred for 2 days. The reaction solution was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. This extract was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (590 mg).

^{1}H-NMR ($CDCl_3$) δ: 0.76 (3H, s), 0.87 (3H, s), 1.83-1.96 (2H, m), 2.14 (2H, t, J = 7.3 Hz), 3.03-3.20 (2H, m), 3.23-3.43 (2H, m), 3.50 (3H, s), 3.68 (1H, d, J = 14.1 Hz), 3.83 (3H, s), 4.07-4.25 (3H, m), 4.35 (1H, d, J = 14.1 Hz), 4.57 (1H, s), 6.10 (1H, s), 6.26 (1H, d, J = 2.6 Hz), 6.59

(1H, d, J = 3.3, 5.9 Hz), 7.09-7.18 (2H, m), 7.50 (1H, dd, J = 2.5, 8.7 Hz), 7.70 (1H, d, J = 8.9Hz), 7.77 (1H, s).

Example 42

1-(carboxymethyl)-3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1H-pyrazol-4-carboxylic acid



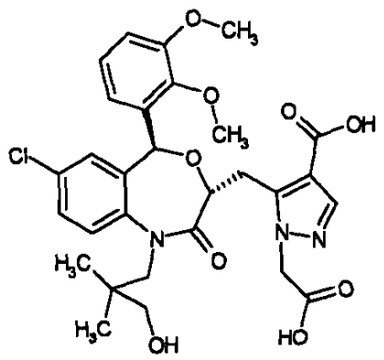
According to a similar manner to that of Example 40, the title compound was obtained.

^{1}H-NMR (DMSO-d_6) δ: 0.76 (3H, s), 0.84 (3H, s), 3.00-3.21 (2H, m), 3.22-3.57 (5H, m), 3.65 (1H, d, J = 14.0 Hz), 3.82 (3H, s), 4.23-4.40 (2H, m), 4.50 (2H, s), 6.06 (1H, s), 6.31 (1H, d, J = 2.5 Hz), 6.96 (1H, d, J = 7.0 Hz), 7.05-7.22 (2H, m), 7.49 (1H, dd, J = 2.1, 8.7 Hz), 7.68 (1H, d, J = 8.9 Hz), 7.99 (1H, s).

Example 43

1-(carboxymethyl)-5-{[(3R,5S)-7-chloro-5-(2,3-

dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1H-pyrazol-4-carboxylic acid

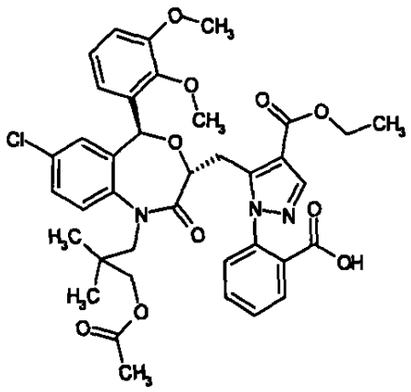


According to a similar manner to that of Example 41, the title compound was obtained.

^{1}H-NMR (DMSO-d_6) δ: 0.75 (3H, s), 0.87 (3H, s), 3.03-3.20 (2H, m), 3.24-3.41 (2H, m), 3.51 (3H, s), 3.66 (1H, d, J = 14.1 Hz), 3.84 (3H, s), 4.10-4.18 (1H, m), 4.33 (1H, d, J = 14.1 Hz), 4.51-4.60 (1H, m), 5.00 (2H, s), 6.11 (1H, s), 6.28 (1H, d, J = 2.6 Hz), 6.72 (1H, dd, J = 2.0, 7.3 Hz), 7.11-7.22 (2H, m), 7.50 (1H, dd, J = 2.5, 8.7 Hz), 7.69 (1H, d, J = 8.9 Hz), 7.77 (1H, s).

Example 44

2-[5-({(3R,5S)-1-[3-(acetyloxy)-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl}methyl)-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]benzoic acid

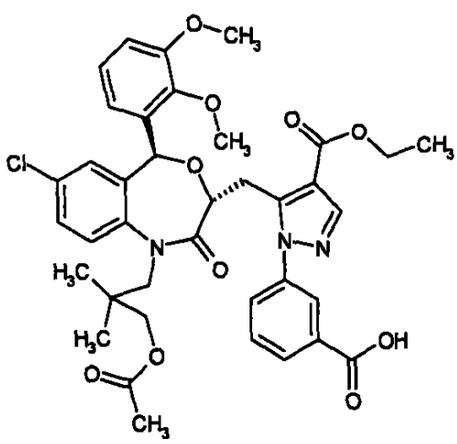


1,1-Dimethoxy-N,N-dimethylmethaneamine (0.598 ml) was added to a solution of ethyl 4-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-3-oxobutanoate (2 g) in toluene (20 ml) and the mixture was refluxed overnight. After the mixture was concentrated under reduced pressure, ethanol (20 ml) and 2-hydrazinobenzoic acid (0.567 g) were added to the residue and the mixture was refluxed for 3 hours. After concentration under reduced pressure, the residue was purified by silica gel column chromatography to obtain the title compound (0.83 g).

^{1}H-NMR (DMSO-d_6) δ: 0.83-0.87 (6H, m), 1.11 (3H, t, J = 7.1 Hz), 1.89 (3H, s), 3.18-3.31 (2H, m), 3.45 (3H, s), 3.56-3.71 (3H, m), 3.83 (3H, s), 3.99-4.16 (3H, m), 4.26 (1H, d, J = 14.3 Hz), 6.00 (1H, s), 6.25 (1H, d, J = 2.3 Hz), 6.67 (1H, dd, J = 1.4, 7.3 Hz), 7.09-7.21 (2H, m), 7.38-7.45 (1H, m), 7.46-7.64 (4H, m), 7.83 (1H, d, J = 8.1 Hz), 7.97 (1H, s).

Example 45

3-(5-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-4-(ethoxycarbonyl)-1H-pyrazol-1-yl)benzoic acid

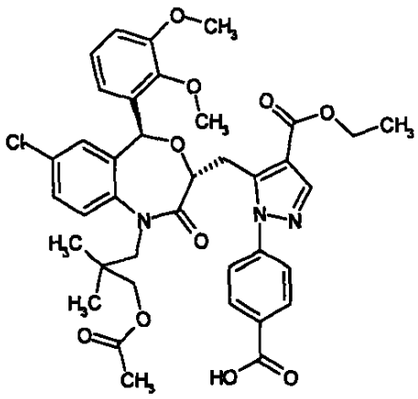


According to a similar manner to that of Example 44, the title compound was obtained.

^{1}H-NMR (DMSO-d_6) δ: 0.85 (3H, s), 0.87 (3H, s), 1.04-1.11 (3H, m), 1.87 (3H, s), 3.28-3.38 (1H, m), 3.45 (3H, s), 3.46-3.75 (4H, m), 3.82 (3H, s), 4.10 (3H, m), 4.32 (1H, d, J = 14.3 Hz), 6.01 (1H, s), 6.20 (1H, d, J = 2.5 Hz), 6.46 (1H, dd, J = 2.6, 6.6 Hz), 7.07-7.15 (2H, m), 7.47-7.59 (2H, m), 7.68 (1H, d, J = 8.9 Hz), 7.73-7.79 (1H, m), 7.93-7.98 (1H, m), 8.02 (1H, t, J = 1.8 Hz), 8.10 (1H, s).

Example 46

4-(5-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-4-(ethoxycarbonyl)-1H-pyrazol-1-yl)benzoic acid



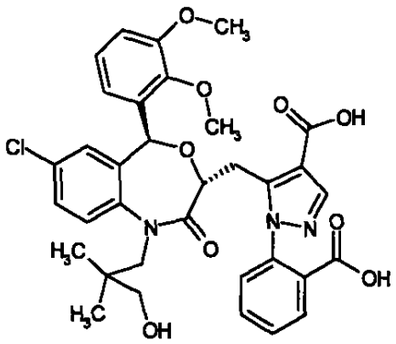
According to a similar manner to that of Example 44, the title compound was obtained.

^{1}H-NMR (DMSO-d_6) δ: 0.86 (s, 6H), 1.10 (3H, t, J = 7.1 Hz), 1.87 (3H, s), 3.38 (1H, d, J = 4.0 Hz), 3.44 (3H, s), 3.53-3.74 (4H, m), 3.82 (3H, s), 4.03-4.15 (3H, m), 4.32 (1H, d, J = 14.3 Hz), 5.99 (1H, s), 6.22 (1H, d, J = 2.5 Hz), 6.46 (1H, dd, J = 2.1, 7.0 Hz), 7.09-7.19 (2H, m), 7.46 (1H, dd, J = 8.7, 2.5 Hz), 7.58-7.69 (3H, m), 7.94 (2H, d, J = 8.5 Hz), 8.11 (1H, s).

Example 47

1-(2-carboxyphenyl)-5-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1H-

pyrazol-4-carboxylic acid



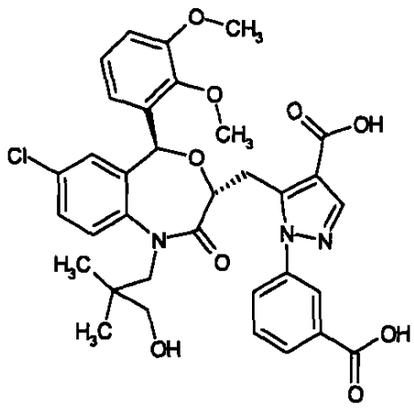
A 1N aqueous sodium hydroxide solution (3.4 ml) was added to a solution of 2-(5-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-4-(ethoxycarbonyl)-1H-pyrazol-1-yl)benzoic acid (0.5 g) obtained in Example 44 in ethanol (5 ml) and the mixture was stirred overnight. The reaction solution was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. This extract was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (0.28 g).

^{1}H-NMR (DMSO-d_6) δ: 0.70 (3H, s), 0.79 (3H, s), 2.96-3.12 (2H, m), 3.22-3.37 (2H, m), 3.46 (3H, s), 3.56 (1H, d, J = 14.0 Hz), 3.83 (3H, s), 4.21 (1H, d, J = 14.0 Hz), 4.50 (1H, t, J = 5.2 Hz), 5.95 (1H, s), 6.24 (1H, d, J = 2.5 Hz), 6.69 (1H, dd, J = 1.6, 7.4 Hz), 7.08-7.23 (2H, m), 7.36-

7.42 (1H, m), 7.44-7.58 (4H, m), 7.76-7.85 (1H, m), 7.91 (1H, s).

Example 48

1-(3-carboxyphenyl)-5-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1H-pyrazol-4-carboxylic acid

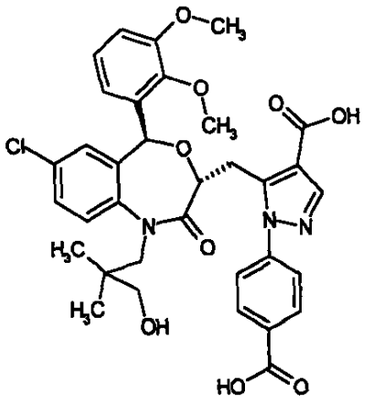


According to a similar manner to that of Example 47, the title compound was obtained.

^{1}H-NMR (DMSO-d_6) δ: 0.70 (3H, s), 0.81 (3H, s), 2.98-3.14 (2H, m), 3.46 (3H, s), 3.48-3.66 (2H, m), 3.82 (3H, s), 4.20 (1H, dd, J = 3.9, 9.6 Hz), 4.28 (1H, d, J = 14.1 Hz), 5.96 (1H, s), 6.19 (1H, d, J = 2.5 Hz), 6.46 (1H, dd, J = 2.5, 6.7 Hz), 7.10 (2H, m), 7.43-7.65 (4H, m), 7.71-7.78 (1H, m), 7.94 (1H, d, J = 7.9 Hz), 8.02-8.06 (2H, m).

Example 49

1-(4-carboxyphenyl)-5-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1H-pyrazol-4-carboxylic acid

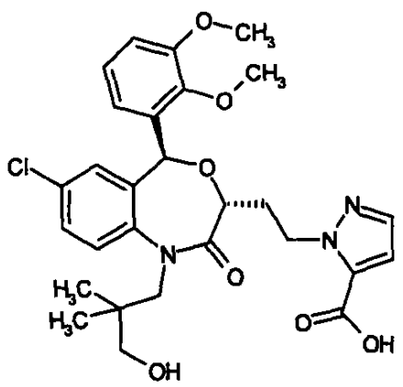


According to a similar manner to that of Example 47, the title compound was obtained.

^{1}H-NMR (DMSO-d_6) δ: 0.70 (3H, s), 0.80 (3H, s), 2.97-3.13 (2H, m), 3.45 (3H, s), 3.56-3.70 (2H, m), 3.82 (3H, s), 4.07 (1H, dd, J = 3.9, 9.8 Hz), 4.23-4.32 (1H, m), 4.51 (1H, t, J = 4.9 Hz), 5.93 (1H, s), 6.20 (1H, d, J = 2.5 Hz), 6.47 (1H, dd, J = 1.8, 7.1 Hz), 7.07-7.20 (2H, m), 7.41 (1H, dd, J = 2.5, 8.7 Hz), 7.54-7.64 (3H, m), 7.92 (2H, d, J = 8.7 Hz), 8.06 (1H, s).

Example 50

1-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrazol-5-carboxylic acid



(1) [(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetic acid (10 g, 19.2 mmol) was dissolved in THF (80 ml), and N-methylmorpholine (2.2 ml, 23.1 mmol) and ethyl chlorocarbonate (2.54 ml, 23.1 mmol) were added dropwide under ice-cooling thereto. After stirring at the same temperature for 1 hour, the mixture was cooled to -30°C and sodium borohydrate (2.18 g, 58.0 mmol) was added thereto. Further, MeOH (80 ml) was added dropwise gradually and the mixture was stirred for 1 hour. At the same temperature, an aqueous saturated ammonium chloride solution was added thereto and the mixture was extracted with AcOEt (480 ml). The organic layer was washed with water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (2:3)] to obtain

(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-ethanol (9.3 g) as a colorless crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.03 (3H, s), 2.03 (3H, s), 2.05-2.30 (2H, m), 3.57 (1H, d, J = 13.8 Hz), 3.63 (3H, s), 3.70-3.93 (7H, m), 4.10 (1H, t, J = 6.2 Hz), 4.55 (1H, d, J = 13.8 Hz), 6.28 (1H, s), 6.64 (1H, d, J = 2.2 Hz), 6.93-7.05 (1H, m), 7.15-7.23 (2H, m), 7.31 (1H, s), 7.31 (1H, dd, J = 2.2, 8.8 Hz).

(2) Under nitrogen atmosphere, n-tributylphosphine (0.74 ml, 2.96 mmol) and 1,1'-azodicarbonyldipiperidine (0.75 g, 2.96 mmol) were added to a solution of (3R,5S)-1-(3-acetoxyl-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-ethanol (1.0 g, 1.98 mmol) obtained in Example 50-(1), methyl 1H-pyrazol-5-carboxylate (0.25 g, 1.98 mmol) and toluene (20 ml) and the mixture was stirred at room temperature for 8 hours. After hexane (10 ml) was added thereto, the mixture was stirred for 30 minutes and then filtered to remove insoluble substances. The filtrate was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (70:30-65:35)] to obtain methyl 1-{2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-

1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrazol-5-carboxylate (0.81 g) as colorless noncrystalline powder from a first eluted fraction and methyl 1-{2-[(3R,5S)-(1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrazol-3-carboxylate (0.17 g) as colorless powder from a second eluted fraction.

First eluted fraction

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.02 (3H, s), 2.02 (3H, s), 2.30-2.41 (2H, m), 3.50 (1H, d, J = 14.1 Hz), 3.60 (3H, s), 3.73 (1H, d, J = 11.4 Hz), 3.77 (1H, t, J = 6.6 Hz), 3.82 (3H, s), 3.84 (1H, d, J = 11.4 Hz), 3.88 (3H, s), 4.55 (1H, d, J = 14.1 Hz), 4.65-4.75 (2H, m), 6.24 (1H, s), 6.60 (1H, d, J = 2.4 Hz), 6.74 (1H, d, J = 2.1 Hz), 6.97 (1H, dd, J = 1.5, 8.1 Hz), 7.10-7.27 (3H, m), 7.30 (1H, dd, J = 2.4, 8.4 Hz), 7.35 (1H, d, J = 2.1 Hz).

Second eluted fraction

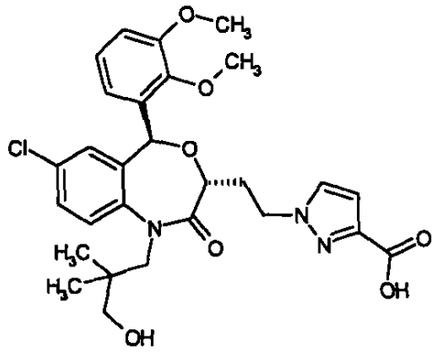
^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.01 (3H, s), 2.02 (3H, s), 2.30-2.45 (2H, m), 3.50 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.71 (1H, d, J = 11.1 Hz), 3.78 (1H, t, J = 6.9 Hz), 3.84 (1H, d, J = 11.1 Hz), 3.89 (6H, s), 4.28-4.50 (2H, m), 4.51 (1H, d, J = 14.1 Hz), 6.24 (1H, s), 6.62 (1H, d, J = 2.4 Hz), 6.71 (1H, d, J = 2.4 Hz), 6.95-7.02 (1H, m), 7.18-7.22 (2H, m), 7.26 (1H, d, J = 8.7 Hz), 7.32 (1H, dd, J = 2.4, 8.7 Hz), 7.37 (1H, d, J = 2.4 Hz)

(3) A mixture of methyl 1-{2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrazol-5-carboxylate (0.72 g, 1.17 mmol) obtained in Example 50-(2), a 1N aqueous sodium hydroxide solution (4.0 ml) and ethanol (14 ml) was stirred at room temperature for 3 hours. This mixture was acidified with 1N hydrochloric acid (5.0 ml) and ethyl acetate (150 ml) was added. The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting crystal was recrystallized with ethyl acetate-hexane to obtain 1-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrazol-5-carboxylic acid (0.63 g) as a colorless crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 2.28-2.50 (2H, m), 3.16 (1H, d, J = 12.3 Hz), 3.35 (1H, d, J = 14.4 Hz), 3.60 (3H, s), 3.62 (1H, d, J = 12.3 Hz), 3.79 (1H, t, J = 6.6 Hz), 3.88 (3H, s), 4.43 (1H, d, J = 14.4 Hz), 4.59-4.81 (2H, m), 6.12 (1H, s), 6.58 (1H, d, J = 2.1 Hz), 6.84 (1H, d, J = 2.1 Hz), 6.97 (1H, dd, J = 1.5, 7.8 Hz), 7.20 (1H, t, J = 7.8 Hz), 7.21-7.29 (2H, m), 7.32 (1H, dd, J = 2.1, 8.7 Hz), 7.40 (1H, d, J = 2.1 Hz).

Example 51

1-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrazol-3-carboxylic acid



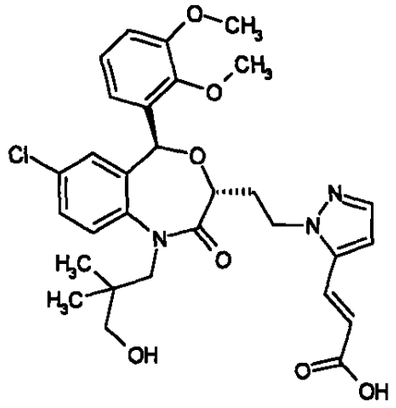
A mixture of methyl 1-{2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrazol-3-carboxylate (0.17 g, 0.28 mmol) obtained in Example 50-(2), a 1N aqueous sodium hydroxide solution (1.0 ml) and ethanol (5 ml) was stirred at room temperature for 3 hours. Further, a 1N aqueous sodium hydroxide solution (1.5 ml) was added and the mixture was stirred for 3 hours. This mixture was acidified with 1N hydrochloric acid (2.8 ml) and ethyl acetate (80 ml) was then added. The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting crystal was recrystallized with ethyl acetate-hexane to obtain 1-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-

2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrazol-3-carboxylic acid (0.12 g) as a colorless crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.63 (3H, s), 1.05 (3H, s), 2.30-2.50 (2H, m), 3.15 (1H, d, J = 11.1 Hz), 3.36 (1H, d, J = 14.4 Hz), 3.60 (1H, d, J = 11.1 Hz), 3.61 (3H, s), 3.82 (1H, t, J = 6.6 Hz), 3.90 (3H, s), 4.30-4.50 (3H, m), 6.15 (1H, s), 6.61 (1H, s), 6.75-6.87 (1H, m), 7.15-7.50 (5H, m).

Example 52

(2E)-3-(1-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)ethyl]-1H-pyrazol-5-yl}acrylic acid



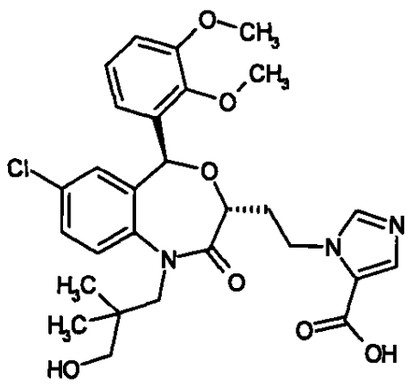
According to a similar manner to that of Example 19, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 1.26 (3H, t, J = 7.0 Hz), 2.29-2.45 (2H, m), 3.15 (1H, d, J = 11.8 Hz), 3.36 (1H, d, J = 14.2 Hz), 3.64 (1H, d, J = 11.8 Hz),

3.36 (1H, d, J = 14.2 Hz), 3.64 (1H, d, J = 11.8 Hz), 3.65 (3H, s), 3.85 (1H, t, J = 6.2 Hz), 3.90 (3H, s), 4.21-4.40 (2H, m), 4.44 (1H, d, J = 14.2 Hz), 6.15 (1H, s), 6.32 (1H, d, J = 16.0 Hz), 6.41 (1H, d, J = 2.2 Hz), 6.60 (1H, d, J = 1.8 Hz), 6.95-7.10 (1H, m), 7.16-7.30 (2H, m), 7.26-7.41 (3H, m), 7.64 (1H, d, J = 16.0 Hz).

Example 53

1-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-imidazol-5-carboxylic acid



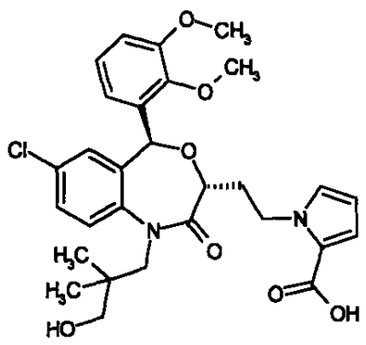
According to a similar manner to that of Example 50, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 2.29-2.40 (2H, m), 3.15 (1H, d, J = 12.0 Hz), 3.36 (1H, d, J = 14.1 Hz), 3.60 (1H, d, J = 12.0 Hz), 3.61 (3H, s), 3.85 (1H, t, J = 7.5 Hz), 3.89 (3H, s), 4.44 (1H, d, J = 14.1 Hz), 6.14 (1H, s), 6.61 (1H, d, J = 2.1 Hz), 6.98-7.02 (1H, m),

7.13-7.26 (2H, m), 7.28 (1H, d, J = 8.7 Hz), 7.34 (1H, dd, J = 2.1, 8.7 Hz), 7.64 (1H, s), 7.77 (1H, s).

Example 54

1-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrrol-2-carboxylic acid



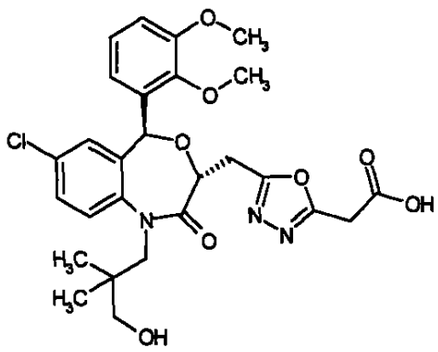
According to a similar manner to that of Example 50, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 2.21-2.39 (2H, m), 3.14 (1H, d, J = 11.4 Hz), 3.35 (1H, d, J = 14.4 Hz), 3.61 (1H, d, J = 11.4 Hz), 3.61 (3H, s), 3.75 (1H, t, J = 6.9 Hz), 3.89 (3H, s), 4.30-4.61 (2H, m), 4.44 (1H, d, J = 14.4 Hz), 6.05-6.10 (1H, m), 6.13 (1H, s), 6.60 (1H, d, J = 2.1 Hz), 6.81-6.90 (1H, m), 6.94-7.03 (2H, m), 7.15-7.30 (3H, m), 7.32 (1H, dd, J = 2.1, 8.7 Hz).

Example 55

(5-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-

2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3,4-oxadiazol-2-yl)acetic acid



(1) Pivaloyl chloride (2.8 ml) was added to a solution of 2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetic acid (10 g) and triethylamine (3.2 ml) in THF (100 ml) at 0°C and the mixture was stirred at 0°C for 30 minutes. To the reaction solution at 0°C, ethyl 3-hydrazino-3-oxopropionate (3.5 g) was added and triethylamine (3.2 ml) was then added dropwise. The mixture was stirred at room temperature for 2 hours and the reaction solution was diluted with ethyl acetate (50 ml). This extract was washed with 0.1N hydrochloric acid, a 5% aqueous potassium hydrogen sulfate solution, an aqueous saturated sodium hydrogen carbonate solution and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain ethyl 3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-

dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}hydrazino)-3-oxopropionate (2.5 g) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.00 (3H, s), 1.25 (3H, t, J = 7.2 Hz), 2.02 (3H, s), 2.70-2.77 (1H, m), 2.92-3.00 (1H, m), 3.39 (2H, s), 3.53 (1H, d, J = 14.2 Hz), 3.60 (3H, s), 3.69-3.87 (2H, m), 3.88 (3H, s), 4.19 (2H, q, J = 7.2 Hz), 4.22-4.39 (1H, m), 4.54 (1H, d, J = 14.4 Hz), 6.25 (1H, s), 6.63 (1H, d, J = 1.8 Hz), 6.96-6.99 (1H, s), 7.15-7.24 (2H, m), 7.28-7.35(2H, m).

(2) Phosphorus oxychloride (0.8 ml) was added to a solution of ethyl 3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}hydrazino)-3-oxopropionate (3.7 g) obtained in Example 55-(1) in DMF (50 ml) and the mixture was refluxed overnight. The reaction solution was concentrated under reduced pressure, poured into an aqueous potassium carbonate solution, and extracted with ethyl acetate. This extract was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain ethyl 5-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]methyl}-

1,3,4-oxadiazol-2-yl)acetate (1.2 g) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 1.26 (3H, t, J = 6.9 Hz), 2.03 (3H, s), 3.31-3.57 (3H, m), 3.61 (3H, s), 3.75-3.87 (2H, m), 3.88 (3H, s), 3.91 (2H, s), 4.17 (2H, q, J = 6.9 Hz), 4.46-4.57 (2H, m), 6.30 (1H, s), 6.61 (1H, d, J = 2.1 Hz), 6.95-6.98 (1H, m), 7.05-7.19 (2H, m), 7.33-7.34(2H, m).

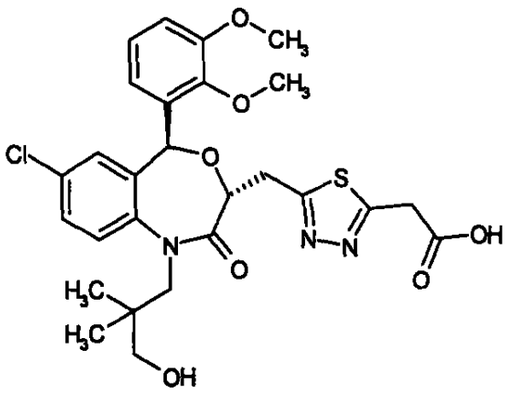
(3) A mixture of ethyl 5-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]methyl}-1,3,4-oxadiazol-2-yl)acetate (1.1 g) obtained in Example 55-(2), a 1N aqueous sodium hydroxide solution (9.35 ml) and methanol (20 ml) was stirred at room temperature for 30 minutes. This mixture was diluted with water (50 ml), acidified, and extracted with chloroform (50 ml) twice. This extract was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain (5-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3,4-oxadiazol-2-yl)acetic acid (0.19 g) as a white crystal.

^{1}H-NMR (DMSO-d_6) δ: 0.63 (3H, s), 0.92 (3H, s), 3.12-3.16(2H, m), 3.38-3.44 (2H, m), 3.56 (3H, s), 3.61-3.79 (2H,

m), 3.85 (3H, s), 4.24-4.50 (3H, m), 6.14 (1H, s), 6.55 (1H, s), 6.92-6.95 (1H, m), 7.12-7.17 (2H, m), 7.31-7.37(2H, m).

Example 56

(5-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3,4-thiadiazol-2-yl)acetic acid



(1) A solution of ethyl 3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}hydrazino))-3-oxopropionate (1.0 g) obtained in Example 55-(1) and Lawesson's reagent (0.96 g) in THF (50 ml) was stirred at 80°C for 1 hour. The reaction solution was poured into water, followed by extraction with ethyl acetate. This extract was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain

ethyl 5-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]methyl}-1,3,4-thiadiazol-2-yl)acetate (0.8 g) as a white amorphous crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 1.30 (3H, t, J = 7.0 Hz), 2.03 (3H, s), 3.51-3.58 (1H, m), 3.62 (3H, s), 3.66-3.87 (4H, m), 3.89 (3H, s), 4.11-4.16 (2H, m), 4.24 (2H, q, J = 7.0 Hz), 4.35 (1H, t, J = 6.4 Hz), 4.55 (1H, d, J = 14.3 Hz), 6.32 (1H, s), 6.61 (1H, d, J = 1.9 Hz), 6.99 (1H, dd, J = 2.3, 7.5 Hz), 7.17-7.20 (2H, m), 7.30-7.32(2H, m).

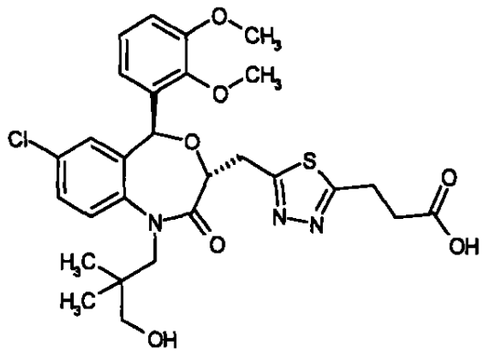
(2) A mixture of ethyl 5-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]methyl}-1,3,4-thiadiazol-2-yl)acetate (0.9 g) obtained in Example 56-(1), a 1N aqueous saturated sodium hydroxide solution (8.0 ml) and methanol (20 ml) was stirred at room temperature for 30 minutes. This mixture was diluted with water (50 ml), acidified, and extracted with chloroform (50 ml) twice. This extract was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain ethyl 5-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-

tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]methyl}-1,3,4-thiadiazol-2-yl)acetate (0.19 g) as a white crystal.

^{1}H-NMR (DMSO-d_6) δ: 0.76 (3H, s), 0.84 (3H, s), 3.06-3.18 (2H, m), 3.35-3.49 (2H, m), 3.52 (3H, s), 3.66-3.71 (1H, m), 3.78 (2H, s), 3.84 (3H, s), 4.26-4.35 (2H, m), 6.14 (1H, s), 6.38 (1H, d, J = 2.3 Hz), 7.06-7.22 (3H, m), 7.51-7.55 (1H, m), 7.71(1H, d, J = 9.0 Hz).

Example 57

3-(5-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxyl-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3,4-thiadiazol-2-yl)propionic acid



(1) Pivaloyl chloride (2.8 ml) was added to a solution of 2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetic acid (10 g) and triethylamine (3.2 ml) in THF (100 ml) at 0°C and the mixture was stirred at 0°C for 30 minutes. to the reaction solution at 0°C, ethyl

4-hydrazino-4-oxobutanoate (3.7 g) was added and triethylamine (3.2 ml) was then added dropwise. After stirring at room temperature for 2 hours, the reaction solution was diluted with ethyl acetate (50 ml). This diluted solution was washed with 0.1N hydrochloric acid, a 5% aqueous potassium hydrogen sulfate solution, an aqueous saturated sodium hydrogen carbonate solution and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain ethyl 4-({2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]acetyl}hydrazino)-4-oxobutanoate (3.6 g) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.00 (3H, s), 1.25 (3H, t, J = 7.2 Hz), 2.03 (3H, s), 2.54 (3H, t, J = 6.4 Hz), 2.66-2.75 (3H, m), 2.89-2.97 (1H, m), 3.54 (1H, d, J = 14.3 Hz), 3.61 (3H, s), 3.69-3.88 (2H, m), 3.89 (3H, s), 4.15 (2H, q, J = 7.2 Hz), 4.33-4.38 (1H, m), 4.54 (1H, d, J = 13.9 Hz), 6.26 (1H, s), 6.64 (1H, d, J = 1.9 Hz), 6.97-7.00 (1H, s), 7.16-7.23 (2H, m), 7.32-7.36(2H, m), 8.11 (1H, brd), 8.31 (1H, brd).

(2) A solution of ethyl 4-({2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-

yl]acetyl}hydrazino)-4-oxobutanoate (1.0 g) obtained in Example 57-(1) and Lawesson's reagent (0.92 g) in THF (50 ml) was stirred at 80°C for 1 hour. The reaction solution was poured into water and then extracted with ethyl acetate. This extract was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain ethyl 3-(5-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3,4-thiadiazol-2-yl)propionate (0.7 g) as white powder.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 1.29 (3H, t, J = 7.2 Hz), 2.03 (3H, s), 2.85 (2H, t, J = 7.4 Hz), 3.37 (3H, t, J = 7.4 Hz), 3.48-3.55 (2H, m), 3.62 (3H, s), 3.65-3.87 (2H, m), 3.90 (3H, s), 4.15 (2H, q, J = 7.2 Hz), 4.35 (1H, t, J = 6.4 Hz), 4.54 (1H, d, J = 14.3 Hz), 6.31 (1H, s), 6.61 (1H, d, J = 2.3 Hz), 6.98-7.01 (1H, m), 7.13-7.23 (2H, m), 7.28-7.35(2H, m).

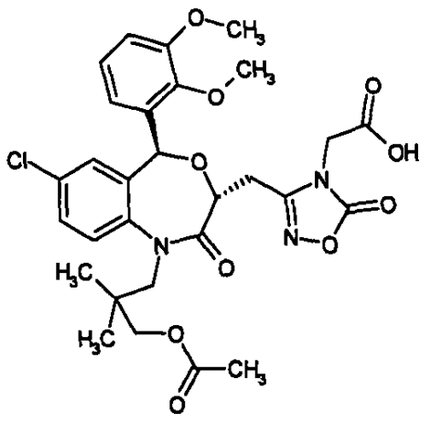
(3) A mixture of ethyl 3-(5-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3,4-thiadiazol-2-yl)propionate (0.7 g) obtained in Example 57-(2), a 1N aqueous sodium hydroxide solution (8.0 ml) and methanol (20 ml) was stirred at room temperature for 30

minutes. This mixture was diluted with water (50 ml), acidified, and extracted with chloroform (50 ml) twice. This extract was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain 3-(5-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxyl-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3,4-thiadiazol-2-yl)propionic acid (0.19 g) as a white crystal.

^{1}H-NMR (DMSO-d_6) δ: 0.78 (3H, s), 0.88 (3H, s), 2.75 (3H, t, J = 7.0 Hz), 3.08-3.20 (2H, m) 3.26 (3H, t, J = 7.0 Hz), 3.49-3.52 (1H, m), 3.53 (3H, s), 3.67-3.81 (1H, m), 3.85 (3H, s), 4.27-4.37 (2H, m) 4.58 (1H, brs), 6.16 (1H, s), 6.40 (1H, d, J = 2.6 Hz), 7.02-7.05 (1H, m), 7.14-7.26 (2H, m), 7.54 (1H, dd, J = 2.6, 8.7 Hz), 7.72(1H, d, J = 8.7 Hz).

Example 58

(3-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-5-oxo-1,2,4-oxadiazol-4(5H)-yl)acetic acid



(1) Triethylamine (10.0 ml, 0.0717 mol) was added to a suspension of hydroxylamine hydrochloride (4.98 g, 0.0717 mol) in DMSO and the mixture was stirred for 30 minutes. The reaction solution was filtered and to the filtrate was added 3-[(3R,5S)-7-chloro-3-(cyanomethyl)-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (7.18 g, 0.0143 mol). The mixture was stirred at 80°C for 18 hours. The reaction solution was extracted with ethyl acetate, washed successively with a 1N aqueous sodium hydroxide solution and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain 3-[(3R,5S)-3-[(2Z)-2-amino-2-(hydroxyimino)ethyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (7.9 g) as an acetone-containing amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.02 (3H, s), 2.03 (3H,

s), 2.59 (1H, dd, J = 6.1, 14.4 Hz), 2.72-2.80 (1H, m), 3.50-3.66 (4H, m), 3.72 (1H, d, J = 11.0 Hz), 3.82-3.88 (1H, m), 3.89 (3H, s), 4.05-4.16 (1H, m), 4.54 (1H, d, J = 14.2 Hz), 4.94 (2H, s), 6.25 (1H, s), 6.62 (1H, d, J = 2.2 Hz), 6.95-7.01 (1H, m), 7.15-7.23 (2H, m), 7.28-7.35 (2H, m).

(2) CDI (1.34 g, 8.24 mmol) and DBU (1.23 ml, 8.24 mmol) were added to a solution of 3-[(3R,5S)-3-[(2Z)-2-amino-2-(hydroxyimino)ethyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (4.0 g, 7.49 mmol) obtained in Example 58-(1) in THF (40 ml) and the mixture was stirred at room temperature for 20 hours. The reaction solution was extracted with ethyl acetate, washed successively with a 1N aqueous hydrochloric acid solution and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (3:2-2:3)] to obtain 3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-3-[(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)methyl]-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (2.53 g) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, s), 1.00 (3H, s), 2.05 (3H, s), 3.01 (1H, dd, J = 4.0, 15.0 Hz), 3.11 (1H, dd, J = 6.9,

15.0 Hz), 3.53 (1H, d, J = 14.2 Hz), 3.65 (3H, s), 3.68 (1H, d, J = 11.2 Hz), 3.89 (3H, s), 3.95 (1H, d, J = 11.2 Hz), 4.20 (1H, dd, J = 4.2, 6.8 Hz), 4.58 (1H, d, J = 14.2 Hz), 6.24 (1H, s), 6.67 (1H, d, J = 2.4 Hz), 7.00 (1H, dd, J = 1.7, 8.1 Hz), 7.10-7.22 (2H, m), 7.29-7.40 (2H, m).

(3) Sodium hydride (46 mg, 1.16 mmol) was added to a solution of 3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-3-[(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)methyl]-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (0.6 g, 0.893 mmol) obtained in Example 58-(2) in DMF under ice-cooling and the mixture was stirred for 30 minutes. To the reaction solution was added tert-butyl bromoacetate and the mixture was stirred for 1.5 hours under ice-cooling and then at room temperature for 30 minutes. After 1N hydrochloric acid was added to the reaction solution, the mixture was extracted with ethyl acetate, washed successively water and an aqueous saturated sodium chloride solution, and then dried over magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (developing solvent: hexane-ethyl acetate (3:1-2:1)) to obtain tert-butyl (3-{[(3R,5S)-1-(3-acetoxy)-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl}methyl)-5-oxo-1,2,4-oxadiazol-4(5H)-ylacetate (0.43 g).

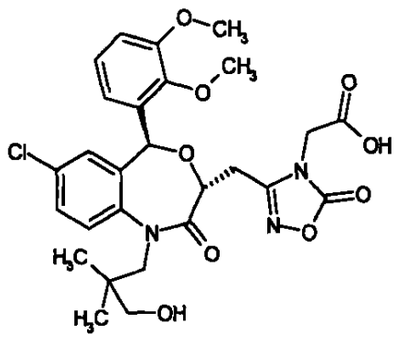
^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.01 (3H, s), 1.47 (9H, s), 2.03 (3H, s), 2.94-3.09 (2H, m), 3.55 (1H, d, J = 14.2 Hz), 3.61 (3H, s), 3.71 (1H, d, J = 11.2 Hz), 3.85 (1H, d, J = 11.0 Hz), 3.89 (3H, s), 4.34-4.39 (3H, m), 4.51 (1H, d, J = 14.2 Hz), 6.28 (1H, s), 6.63 (1H, d, J = 2.2 Hz), 6.97-7.06 (2H, m), 7.19 (1H, t, J = 7.9 Hz), 7.29-7.39 (2H, m).

(4) Trifluoroacetic acid (5 ml) was added to tert-butyl (3-{[(3R,5S)-1-(3-acetyloxy)-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl}methyl)-5-oxo-1,2,4-oxadiazol-4(5H)-ylacetate (0.42 g, 0.616 mmol) obtained in Example 58-(3) under ice-cooling and the mixture was stirred for 30 minutes and then at room temperature for 50 minutes. The reaction solution was concentrated under reduced pressure to obtain [3-{[(3R,5S)-1-(3-acetyloxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-5-oxo-1,2,4-oxadiazol-4(5H)-yl]acetic acid (0.40 g).

^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, s), 0.98 (3H, s), 2.05 (3H, s), 3.05-3.08 (2H, m), 3.54 (1H, d, J = 14.2 Hz), 3.62 (3H, s), 3.73 (1H, d, J = 11.0 Hz), 3.85-3.95 (4H, m), 4.34 (1H, t, J = 11.0 Hz), 4.47-4.54 (3H, m), 6.27 (1H, s), 6.62 (1H, d, J = 2.2 Hz), 6.98-7.39 (6H, m).

Example 59

[3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-5-oxo-1,2,4-oxadiazol-4(5H)-yl]acetic acid



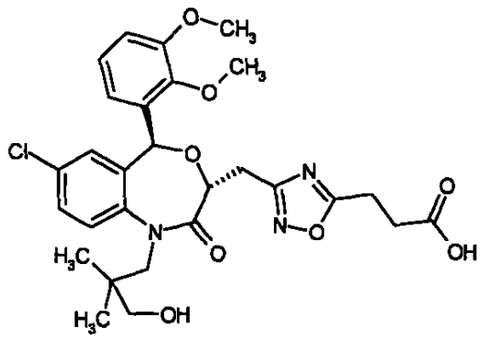
A 1N aqueous sodium hydroxide solution (1.21 ml, 1.21 mmol) was added to a mixture of (3-{[(3R,5S)-1-(3-acetyloxy)-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-5-oxo-1,2,4-oxadiazol-4(5H)-yl)acetic acid (0.25 g, 0.405 mmol) obtained in Example 58 in ethanol-THF (1:1) (3 ml) and the mixture was stirred for 2 hours. The reaction solution was acidified with 1N hydrochloric acid (1.5 ml), extracted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, and then dried over magnesium sulfate. After concentration under reduced pressure, the residue was purified by preparative HPLC to obtain [3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-5-oxo-

1,2,4-oxodiazol-4(5H)-yl]acetic acid (0.16 g).

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 3.09 (2H, d, J = 7.4 Hz), 3.24 (1H, d, J = 12.1 Hz), 3.42 (1H, d, J = 14.6 Hz), 3.58-3.65 (4H, m), 3.87-3.90 (4H, m), 4.34 (1H, t, J = 6.7 Hz), 4.41 (1H, d, J = 14.6 Hz), 4.46 (2H, s), 6.16 (1H, s), 6.61 (1H, d, J = 2.2 Hz), 7.00 (2H, d, J = 8.3 Hz), 7.16-7.43 (3H, m).

Example 60

3-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)propionic acid



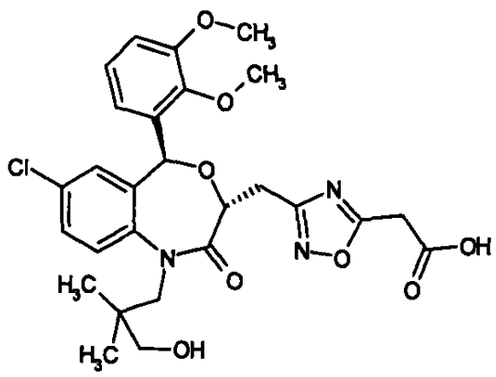
Triethylamine (0.44 ml, 3.18 mmol) and ethyl 4-chloro-4-oxobutyrate (0.29 ml, 2.06 mmol) were added dropwise to a solution of 3-[(3R,5S)-3-[(2Z)-2-amino-2-(hydroxyimino)ethyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (1.0 g, 1.87 mmol) obtained in

Example 58-(1) in THF (10 ml) under ice-cooling and the mixture was stirred at room temperature for 24 hours. After the reaction solution was concentrated under reduced pressure, water (10 ml) was added and the mixture was heated to reflux for 22 hours. The reaction solution was extracted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in ethanol (10 ml) and a 2N aqueous sodium hydroxide solution (3.74 ml, 7.48 mmol) was added thereto. The mixture was then stirred for 2 hours. The reaction solutions was diluted with water and then extracted with diethyl ether. The extract was acidified with 6N hydrochloric acid, extracted with ethyl acetate, washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. After the residue was dissolved in ethanol, active carbon was added thereto and the mixture was stirred for 10 minutes. Insoluble substances were filtered off and the filtrate was concentrated under reduced pressure to obtain 3-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)propionic acid (0.66 g).

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 2.89 (2H, d, J = 7.2 Hz), 3.12-3.27 (4H, m), 3.34-3.43 (2H, m), 3.58-3.67 (4H, m), 3.89 (3H, s), 4.39-4.52 (2H, m), 6.19 (1H, s), 6.60 (1H, d, J = 1.5 Hz), 6.96-7.40 (5H, m).

Example 61

2-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)acetic acid



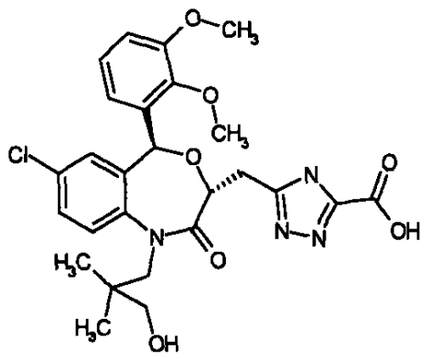
According to a similar manner to that of Example 60, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 3.17-3.44 (4H, m), 3.60-3.67 (4H, m), 3.88 (3H, s), 3.99 (2H, s), 4.43-4.50 (2H, m), 6.18 (1H, s), 6.60 (1H, d, J = 1.5 Hz), 6.96-7.41 (4H, m).

Example 62

3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-

2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1H-1,2,4-triazol-5-carboxylic acid



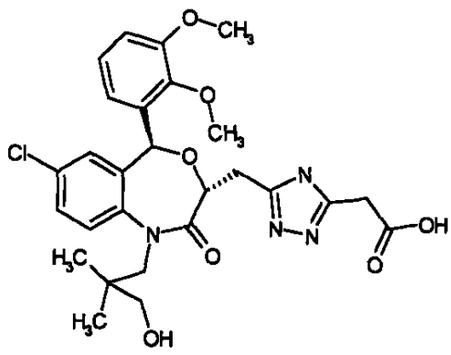
Iodomethane (0.2 ml) was added to a solution of 3-[(3R,5S)-3-(2-amino-2-thioxoethyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (2 g) obtained in Example 16-(2) in acetone (20 ml) and the mixture was stirred overnight. After concentration under reduced pressure, butanol (20 ml) and ethyl hydrazino(oxo)acetate (0.317 g) were added to the residue and the mixture was refluxed for 2 hours. After concentration under reduced pressure, ethanol (20 ml) and a 1N aqueous sodium hydroxide solution (4 ml) were added to the residue and the mixture was stirred overnight. The reaction solution was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. This extract was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was

purified by silica gel column chromatography to obtain the title compound (0.32 g).

^{1}H-NMR ($CDCl_3$) δ: 0.76 (3H, s), 0.86 (3H, s), 3.05-3.22 (3H, m), 3.51 (3H, s), 3.67 (1H, d, J = 14.1 Hz), 3.83 (3H, s), 4.25-4.42 (2H, m), 4.56 (1H, s), 6.11 (1H, s), 6.35 (1H, d, J = 2.5Hz), 6.78 (1H, s), 7.10-7.18 (2H, m) , 7.55 (1H, dd, J = 2.5, 8.9 Hz) , 7.72 (1H, d, J = 8.9 Hz).

Example 63

(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1H-1,2,4-triazol-5-yl)acetic acid

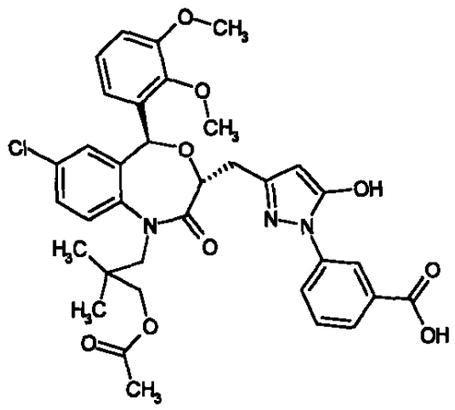


According to a similar manner to that of Example 62, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, s), 0.86 (3H, s), 3.04-3.19 (4H, m), 3.50 (3H, s), 3.65-3.72 (3H, m), 3.83 (3H, s), 4.28-4.40 (2H, m), 6.10 (1H, s), 6.34 (1H, d, J = 2.4Hz), 6.86 (1H, dd, J = 2.3, 7.0 Hz) , 7.09-7.20 (1H, m) , 7.55 (1H, dd, J = 2.4, 8.9 Hz) , 7.71 (1H, d, J = 8.9 Hz).

Example 64

3-[3-({(3R,5S)-1-[3-(acetyloxy)-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3-5-tetrahydro-4,1-benzoxazepin-3-yl}methyl)-5-hydroxy-1H-pyrazol-1-yl]benzoic acid



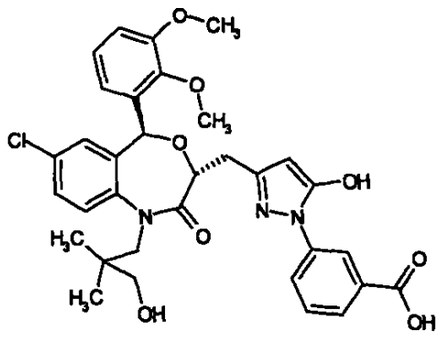
To a solution of ethyl 4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]}-3-oxobutanoate (2 g) obtained in Example 26-(1) in ethanol (20 ml), 3-hydrazinobenzoic acid (0.567 g) was added and the mixture was refluxed overnight. After concentration under reduced pressure, the residue was purified by silica gel column chromatography to obtain the title compound (1.9 g).

^{1}H-NMR (DMSO-d_6) δ: 0.92 (6H, s), 1.99 (3H, s), 2.79-3.07 (2H, m), 3.52 (3H, s), 3.61-3.80 (3H, m), 3.85 (3H, s), 4.19 (1H, t, J = 6.5 Hz), 4.36 (1H, d, J = 14.3 Hz), 5.42 (1H, s), 6.13 (1H, s), 6.39 (1H, d, J = 2.4 Hz), 7.10-7.24

(3H, m), 7.48-7.59 (2H, m), 7.75 (2H, t, J = 9.0 Hz), 7.95 (1H, d, J = 7.9 Hz), 8.28 (1H, s).

Example 65

3-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-5-hydroxy-1H-pyrazol-1-yl)benzoic acid



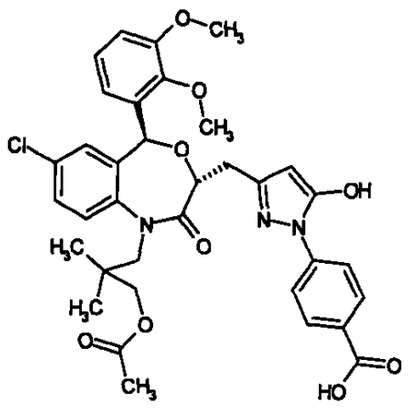
A 1N aqueous sodium hydroxide solution (3.4 ml) was added to a solution of 3-[3-({(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3-5-tetrahdyro-4,1-benzoxazepin-3-yl]methyl}-5-hydroxy-1H-pyrazol-1-yl)benzoic acid (0.9 g) obtained in Example 64 in ethanol (4.5 ml) and the mixture was stirred overnight. The reaction solution was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. This extract was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel

column chromatography to obtain the title compound (0.586 g).

^{1}H-NMR (DMSO-d_6) δ: 0.78 (3H, s), 0.86 (3H, s), 2.78-3.24 (4H, m), 3.53 (3H, s), 3.69 (1H, d, J = 14.1 Hz), 3.85 (3H, s), 4.18 (1H, t, J = 6.5 Hz), 4.32 (1H, d, J = 14.1 Hz), 4.56 (1H, t, J = 4.9 Hz), 5.42 (1H, s), 6.12 (1H, s), 6.39 (1H, d, J = 2.4 Hz), 7.07-7.26 (3H, m), 7.47-7.60 (2H, m), 7.67-7.81 (2H, m), 7.95 (1H, d, J = 8.1 Hz), 8.29 (1H, s).

Example 66

4-[3-({(3R,5S)-1-[3-(acetyloxy)-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl}methyl)-5-hydroxy-1H-pyrazol-1-yl]benzoic acid



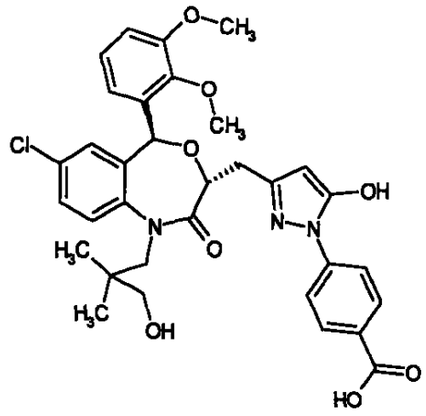
According to a similar manner to that of Example 64, the title compound was obtained.

^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, s), 0.93 (3H, s), 1.99

(3H, s), 2.80-3.05 (2H, m), 3.52 (3H, s), 3.61-3.81 (3H, m), 3.85 (3H, s), 4.17 (1H, t, J = 6.4 Hz), 4.36 (1H, d, J = 14.1Hz), 5.43 (1H, s), 6.13 (1H, s), 7.10-7.23 (3H, m), 7.54 (1H, dd, J = 2.2, 8.6 Hz), 7.75 (d, J = 8.8 Hz), 7.84 (2H, d, J = 8.8Hz), 7.99 (d, J = 8.6 Hz), 8.32 (1H, s).

Example 67

4-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-5-hydroxy-1H-pyrazol-1-yl)benzoic acid



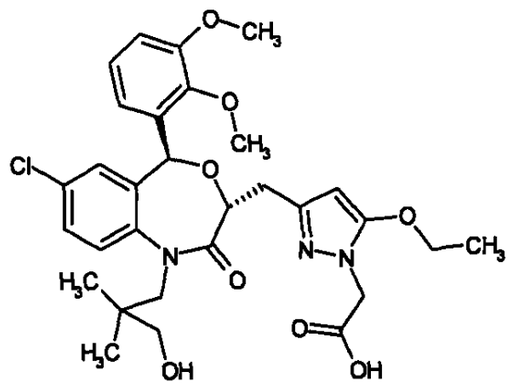
According to a similar manner to that of Example 65, the title compound was obtained.

^{1}H-NMR (DMSO-d_6) δ: 0.78 (3H, s), 0.87 (3H, s), 2.80-3.25 (4H, m), 3.53 (3H, s), 3.69 (1H, d, J = 14.1 Hz), 3.85 (3H, s), 4.16 (1H, t, J = 6.5 Hz), 4.32 (1H, d, J = 14.1 Hz), 4.56 (1H, t, J = 4.8 Hz), 5.43 (1H, s), 6.12 (1H, s) ,6.39 (1H, d, J = 2.4 Hz), 7.09-7.24 (3H, m) 7.53 (1H,

dd, J = 2.4, 8.6 Hz), 7.72 (1H, d, J = 8.8 Hz), 7.85 (2H, d, J = 8.8 Hz), 7.94-8.04 (2H, m).

Example 68

(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-5-ethoxy-1H-pirazol-1-yl)acetic acid



(1) Pyridine (0.3 ml) was added to a solution of ethyl 4-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-3-oxobutanoate (2 g) obtained in Example 26-(1) and ethyl hydrazinoacetate hydrochloride (0.577 g) in ethanol (20 ml) and the mixture was refluxed for 3 hours. After concentration under reduced pressure, the residue was purified by silica gel column chromatography to obtain ethyl (3-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-

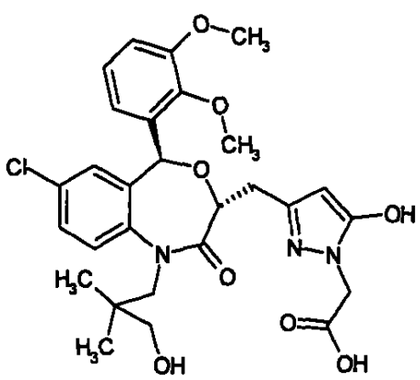
4,1-benzoxazepin-3-yl]methyl}-5-ethoxy-1H-pyrazol-1-yl)acetate (0.62 g) from a first eluted fraction and ethyl [3-({(3R,5S)-1-[3-(acetoxy)-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl}methyl)-5-hydroxy-1H-pyrazol-1-yl]acetate (1.2 g) from a second eluted fraction.

(2) A 1N aqueous sodium hydroxide solution (3.3 ml) was added to a solution of ethyl (3-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-5-ethoxy-1H-pyrazol-1-yl)acetate (0.45 g) obtained in Example 68-(1) in ethanol (4.5 ml) and the mixture was stirred overnight. The reaction solution was neutralized with 1N hydrochloric acid and extracted with chloroform. This extract was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (0.38 g).

^{1}H-NMR ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 1.40 (3H, t, J = 7.0 Hz), 3.02 (1H, dd, J = 6.3, 14.8 Hz), 3.11-3.26 (2H, m), 3.37 (1H, d, J = 14.3 Hz), 3.57-3.70 (4H, m), 3.89 (3H, s), 4.05-4.23 (3H, m), 4.45 (1H, d, J = 14.3 Hz), 4.63 (2H, s), 5.49 (1H, s), 6.17 (1H, s), 6.58 (1H, d, J = 1.8 Hz), 6.98 (1H, dd, J = 2.4, 7.1 Hz), 7.11-7.23 (2H, m), 7.25-7.39 (3H, m).

Example 69

(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-5-hydroxy-1H-pyrazol-1-yl)acetic acid



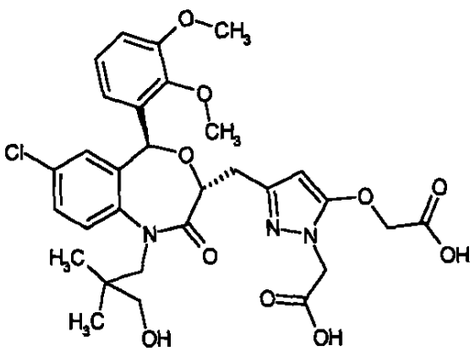
A 1N aqueous sodium hydroxide solution (0.5 ml) was added to a solution of ethyl [3-({(3R,5S)-1-[3-(acetyloxy)-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)methyl)-5-hydroxy-1H-pyrazol-1-yl]acetate (0.1 g) obtained in Example 68-(1) in ethanol (1 ml) and the mixture was stirred overnight. The reaction solution was neutralized with 1N hydrochloric acid and extracted with chloroform-methanol. This extract was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the

title compound (0.042 g).

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.03 (3H, s), 2.84-3.05 (2H, m), 3.11-3.23 (2H, m), 3.32-3.44 (2H, m), 3.62 (3H, s), 3.89 (3H, s), 4.26 (1H, t, J = 6.5 Hz), 4.34-4.49 (2H, m), 4.53-4.63 (1H, m), 6.16 (1H, s), 6.62 (1H, d, J = 2.0 Hz), 6.96-7.04 (1H, m), 7.08-7.25 (3H, m), 7.30-7.43 (3H, m).

Example 70

[5-(carboxymethoxy)-3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1H-pyrazol-1-yl]acetic acid



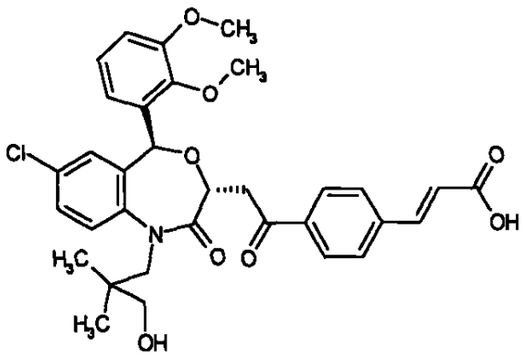
Methyl bromoacetate (0.459 g) and potassium carbonate (0.441 g) were added to a solution of ethyl [3-({(3R,5S)-1-[3-(acetoxy)-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl}methyl)-5-hydroxy-1H-pyrazol-1-yl]acetate (0.5 g) obtained in Example 68-(1) in acetonitrile (5 ml) and the

mixture was stirred overnight. The reaction solution was diluted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. To this residue were added ethanol (5 ml) and a 1N aqueous sodium hydroxide solution (2.78 ml) and the mixture was stirred overnight. The reaction solution was neutralized with 1N hydrochloric acid and extracted with chloroform. This extract was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (0.116 g).

^{1}H-NMR (DMSO-d_6) δ: 0.76 (3H, s), 0.85 (3H, s), 2.83 (2H, m), 3.12 (2H, m), 3.51 (3H, s), 3.65 (1H, m), 3.84 (3H, s), 4.01 (1H, m), 4.32 (1H, d, J = 14.1 Hz), 4.58 (2H, s), 4.66 (2H, s), 5.47 (1H, s), 6.09 (1H, s), 6.35 (1H, d, J = 2.4 Hz), 7.12 (3H, m), 7.51 (1H, dd, J = 2.5, 8.8 Hz), 7.67 (1H, d, J = 8.8 Hz).

Example 71

(2E)-3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)acrylic acid



(1) Oxalyl chloride (10 ml) was added to a solution of (2E)-4-(bromophenyl)-4-oxo-2-butenoic acid (24.5 g) in a mixture of THF (200 ml) and DMF (3 drops) and the mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (120 ml). The resulting solution was added dropwise to a mixed solvent of a solution of 3-({4-chloro-2-[(S)-(2,3-dimethoxyphenyl)(hydroxyl)methyl]phenyl}amino)-2,2-dimethyl-1-propanol (24.5 g) in ethyl acetate (300 ml) and a 1N aqueous sodium hydroxide solution (130 ml) under ice-cooling, and the mixture was stirred at 0°C for 1 hour. The organic layer was washed successively with an aqueous saturated sodium hydrogen carbonate solution and an aqueous saturated sodium chloride solution, dried over sodium sulfate, and then concentrated under reduced pressure. The resulting residue was dissolved in ethanol (240 ml), DBU (11 ml) was added, and the mixture was stirred at room temperature overnight. Water (60 ml) was added to the

reaction solution gradually and the mixture was stirred for 1 hour. Precipitated crystals were filtered and washed with a mixed solution of ethanol/water = 2/1 to obtain (3R,5S)-3-[2-(4-bromophenyl)-2-oxoethyl]-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-1,5-dihydro-4,1-benzoxazepin-2(3H)-one (24.5 g).

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 3.14 (1H, d, J = 12.0 Hz), 3.32 (1H, dd, J = 4.5 Hz, 17.4 Hz), 3.42 (1H, d, J = 14.4 Hz), 3.62 (3H, s), 3.64 (1H, m), 3.81(1H, m), 3.90 (3H, s), 4.48 (1H, d, J = 12.0 Hz), 4.61 (1H, q, J = 4.2 Hz), 6.19 (1H, s), 6.63 (1H, s), 6.99 (1H, dd, J = 2.4 Hz, 7.5 Hz), 7.15 (2H, m), 7.41 (2H, m), 7.61 (2H, d, J = 8.4 Hz), 7.84 (2H, d, J = 8.4 Hz).

(2) Palladium acetate (338 mg), triphenylphosphine (788 mg), ethyl acrylate (2.2 ml) and triethylamine (3.3 ml) were added to a solution of (3R,5S)-3-[2-(4-bromophenyl)-2-oxoethyl]-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-1,5-dihydro-4,1-benzoxazepin-2(3H)-one (6.0 g) obtained in Example 71-(1) in DMF (60 ml) and the mixture was heated at 100°C for 20 hours under nitrogen atmosphere. 1N hydrochloric acid was added to the reaction solution, followed by extraction with ethyl acetate. The extract was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column

chromatography to obtain ethyl (2E)-3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2,-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)acrylate (3.1 g).

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 1.35 (3H, t, J = 7.2 Hz), 3.14 (1H, m), 3.36 (1H, m), 3.43 (1H, m), 3.63 (3H, s), 3.64 (1H, m), 3.81(1H, m), 3.90 (3H, s), 4.48 (1H, d, J = 13.2 Hz), 4.61 (1H, q, J = 3.6 Hz), 6.20 (1H, s), 6.53 (1H, d, J = 16.5 Hz), 6.64 (1H, m), 6.99 (1H, m), 7.16 (2H, m), 7.41 (2H, m), 7.60 (2H, d, J = 8.4 Hz), 7.68 (1H, d, J = 16.5 Hz), 7.98 (2H, d, J = 8.4 Hz).

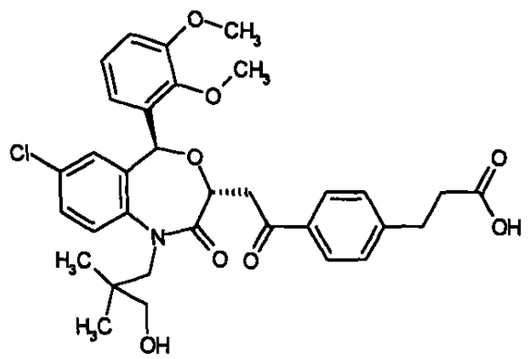
(3) A 2N aqueous sodium hydroxide solution (25 ml) was added to a solution of ethyl (2E)-3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2,-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)acrylate (3.1 g) obtained in Example 71-(2) in a mixture of THF (100 ml) and ethanol (100 ml), and the mixture was stirred at room temperature for 10 hours. After the reaction solution was concentrated under reduced pressure, the residue was dissolved in water and washed with ether. The aqueous layer was acidified with 1N hydrochloric acid and then extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain (2E)-3-(4-{[(3R,5S)-7-chloro-5-(2,3-

dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)-acrylic acid (1.1 g).

^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s), 1.05 (3H, s), 3.15 (1H, d, J = 12.0 Hz), 3.36 (1H, dd, J = 3.9 Hz, 17.1 Hz), 3.43 (1H, d, J = 15.0 Hz), 3.62 (3H, s), 3.66 (1H, m), 3.82(1H, t, J = 9.3 Hz), 3.89 (3H, s), 4.48 (1H, d, J = 14.4 Hz), 4.62 (1H, q, J = 3.9 Hz), 6.19 (1H, s), 6.52 (1H, d, J = 15.9 Hz), 6.63 (1H, s), 6.98 (1H,m), 7.15 (2H, m), 7.40 (2H, m), 7.62 (2H, d, J = 8.4 Hz), 7.77 (1H, d, J = 15.9 Hz), 7.99 (2H, d, J = 8.4 Hz).

Example 72

3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)propionic acid



(1) Raney nickel was added to a solution of ethyl (2E)-3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-

benzoxazepin-3-yl]acetyl}phenyl)acrylate (6.2 g) obtained in Example 71-(2) in a mixture of THF (100 ml) and ethanol (50 ml), and the mixture was stirred at room temperature overnight under hydrogen atmosphere. The catalyst was filtered off with Celite and the filtrate was concentrated under reduced pressure to obtain ethyl 3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)propionate (6.6 g) as a crude crystal, which was used in the next step without purification.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 1.24 (3H, t, J = 7.4 Hz), 2.63 (2H, t, J = 8.4 Hz), 3.00 (2H, t, J = 8.4 Hz), 3.13 (1H, m), 3.33 (1H, m), 3.42 (1H, d, J = 14.6 Hz), 3.62 (3H, s), 3.75 (2H, m), 3.89 (3H, s), 4.21 (1H, m), 4.48 (1H, d, J = 14.6 Hz), 4.62 (1H, q, J = 4.2 Hz), 6.19 (1H, s), 6.63 (1H, m), 6.98 (1H, t, J = 5.0 Hz), 7.18 (2H, m), 7.29 (2H, d, J = 8.0 Hz), 7.40 (2H, m), 7.90 (2H, d, J = 8.0 Hz).

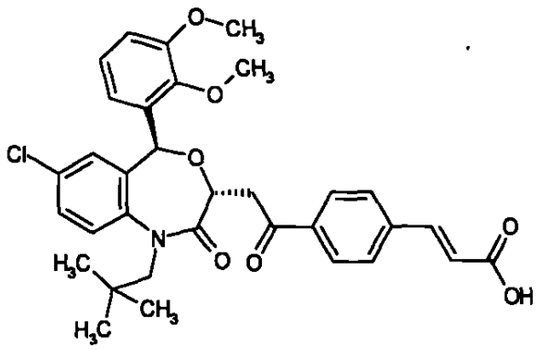
(2) A 2N aqueous sodium hydroxide solution (15 ml) was added to a solution of ethyl 3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)propionate (3.5 g) obtained in Example 72-(1) in a mixture of THF (50 ml) and ethanol (50 ml), and the mixture was stirred at room temperature for 2 hours.

The reaction solution was concentrated under reduced pressure and the residue was dissolved in water and then washed with ether. The aqueous layer was acidified with 1N hydrochloric acid and then extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain 3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)propionic acid(2.2 g).

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 2.70 (2H, t, J = 7.8 Hz), 3.01 (2H, t, J = 7.8 Hz), 3.15 (1H, d, J = 12.0 Hz), 3.33 (1H, dd, J = 4.5 Hz, 17.4 Hz), 3.42 (1H, d, J = 17.4 Hz), 3.62 (3H, s), 3.66 (1H, m), 3.82 (1H, t, J = 8.7 Hz), 3.89 (3H, s), 4.48 (1H, d, J = 14.4 Hz), 4.62 (1H, q, J = 4.2 Hz), 6.19 (1H, s), 6.63 (1H, m), 6.99 (1H, t, J = 5.1 Hz), 7.18 (2H, d, J = 5.1 Hz), 7.30 (2H, d, J = 8.1 Hz), 7.40 (2H, m), 7.91 (2H, d, J = 8.1 Hz).

Example 73

(2E)-3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)acrylic acid

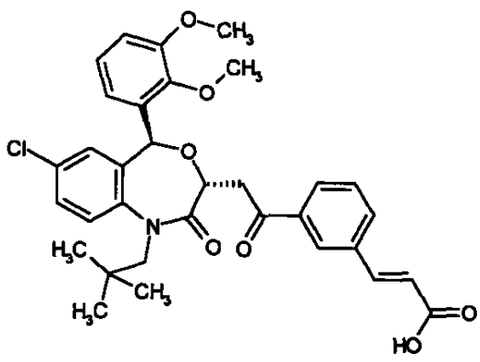


According to a similar manner to that of Example 71, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 3.31 (1H, dd, J = 17.1, 4.8 Hz), 3.41 (1H, d, J = 14.1 Hz), 3.63 (3H, s), 3.80 (1H, t, J = 9.0 Hz), 3.90 (3H, s), 4.51 (1H, d, J = 14.1 Hz), 4.67 (1H, dd, J = 8.4, 4.8 Hz), 6.31 (1H, s), 6.52 (1H, d, J = 16.2 Hz), 6.63 (1H, m), 6.98 (1H, t, J = 4.8 Hz), 7.16 (2H, d, J = 4.5 Hz), 7.37 (2H, m), 7.61 (2H, d, J = 8.1 Hz), 7.76 (1H, d, J = 16.2 Hz), 8.01 (2H, d, J = 8.1 Hz).

Example 74

(2E)-3-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)acrylic acid

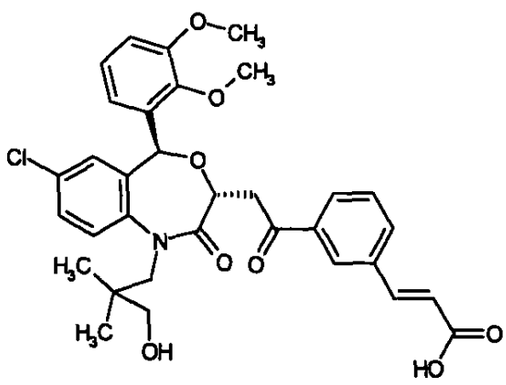


According to a similar manner to that of Example 71, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.96 (9H, s), 3.37 (1H, m), 3.42 (1H, d, J = 14.1 Hz), 3.64 (3H, s), 3.82 (1H, t, J = 8.1 Hz), 3.89 (3H, s), 4.52 (1H, d, J = 14.1 Hz), 4.67 (1H, dd, J = 7.8, 4.5 Hz), 6.32 (1H, s), 6.50 (1H, d, J = 16.2 Hz), 6.64 (1H, m), 6.98 (1H, m), 7.13 (2H, m), 7.36 (2H, m), 7.49 (1H, t, J = 7.5 Hz), 7.72 (1H, d, J = 7.8 Hz), 7.79 (1H, d, J = 16.2 Hz), 8.01 (1H, d, J = 7.5 Hz), 8.17 (1H, s).

Example 75

(2E)-3-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)acrylic acid

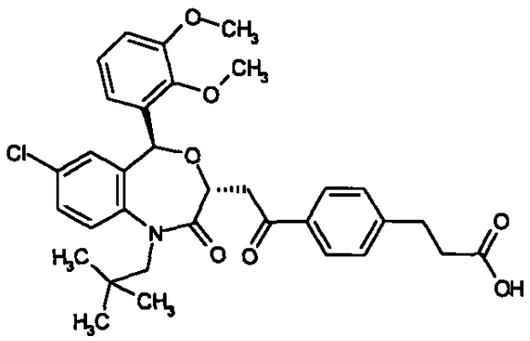


According to a similar manner to that of Example 71, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s), 1.05 (3H, s), 3.16 (1H, d, J = 12.0 Hz), 3.39 (1H, m), 3.44 (1H, d, J = 14.4 Hz), 3.63 (3H, s), 3.66 (1H, m), 3.82(1H, m), 3.90 (3H, s), 4.49 (1H, d, J = 14.4 Hz), 4.64 (1H, q, J = 4.5 Hz), 6.20 (1H, s), 6.52 (1H, d, J = 15.9 Hz), 6.65 (1H, s), 7.00 (1H,m), 7.19 (2H, m), 7.42 (2H, m), 7.51 (1H, t, J = 7.5 Hz), 7.76 (1H, m), 7.79 (1H, d, J = 15.9 Hz), 8.01 (1H, d, J = 7.5 Hz), 8.14 (1H, s).

Example 76

3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)propionic acid

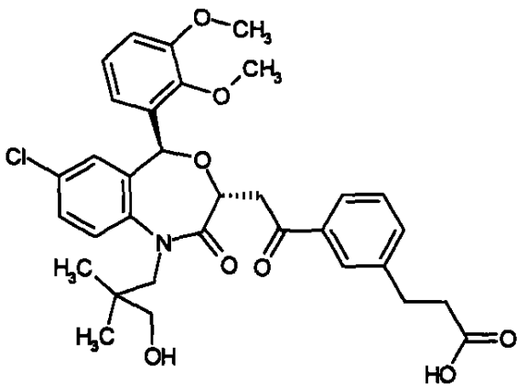


According to a similar manner to that of Example 72, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (9H, s), 2.67 (2H, t, J = 7.5 Hz), 2.99 (2H, t, J = 7.5 Hz), 3.31 (1H, dd, J = 17.4 Hz, 4.5 Hz), 3.40 (1H, d, J = 13.8 Hz), 3.81 (1H, m), 3.89 (3H, s), 4.50 (1H, d, J = 13.8 Hz), 4.65 (1H, q, J = 4.8 Hz), 6.31 (1H, s), 6.63 (1H, m), 6.97 (1H, m), 7.15 (2H, m), 7.28 (2H, d, J = 8.1 Hz), 7.37 (2H, m), 7.92 (2H, d, J = 8.1 Hz).

Example 77

3-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)propionic acid

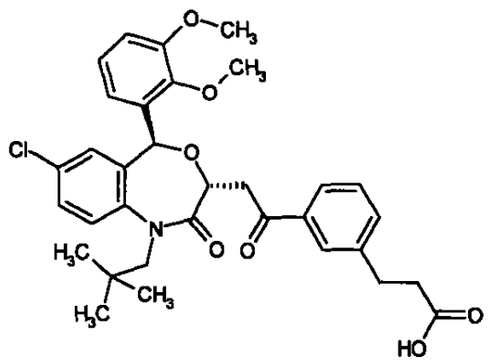


According to a similar manner to that of Example 72, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s), 1.03 (3H, s), 2.65 (2H, t, J = 7.5 Hz), 2.98 (2H, t, J = 7.5 Hz), 3.19 (1H, d, J = 12.0 Hz), 3.37 (1H, dd, J = 4.2 Hz, 16.8 Hz), 3.44 (1H, d, J = 17.4 Hz), 3.62 (3H, s), 3.66 (1H, m), 3.86 (1H, t, J = 9.6 Hz), 3.88 (3H, s), 4.47 (1H, d, J = 12.0 Hz), 4.63 (1H, q, J = 4.5 Hz), 6.19 (1H, s), 6.64 (1H, m), 6.98 (1H, m), 7.18 (2H, m), 7.41 (4H, m), 7.78 (2H, m).

Example 78

3-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)propionic acid

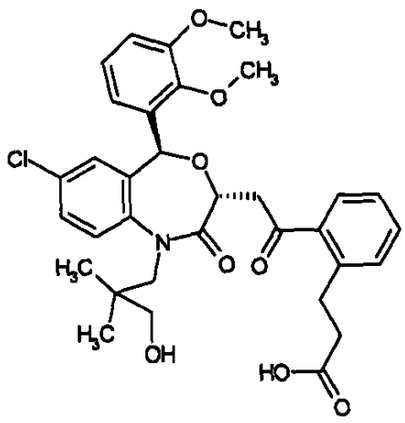


According to a similar manner to that of Example 72, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 2.66 (2H, t, J = 7.5 Hz), 2.98 (2H, t, J = 7.5 Hz), 3.34 (1H, dd, J = 17.1 Hz, 4.8 Hz), 3.40 (1H, d, J = 14.1 Hz), 3.63 (3H, s), 3.65 (1H, m), 3.78 (1H, t, J = 7.8 Hz), 3.88 (3H, s), 4.52 (1H, d, J = 14.1 Hz), 4.65 (1H, q, J = 3.9 Hz), 6.31 (1H, s), 6.63 (1H, m), 6.98 (1H, m), 7.17 (2H, m), 7.38 (4H, m), 7.83 (2H, m).

Example 79

3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)propionic acid

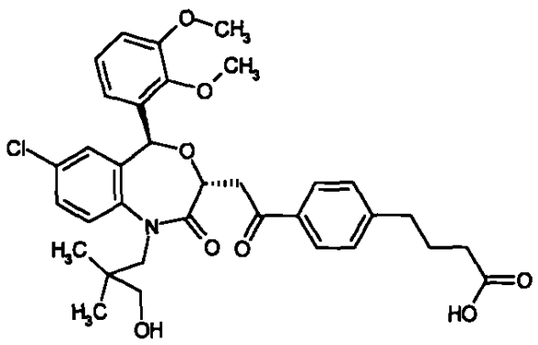


According to a similar manner to that of Example 72, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s), 1.04 (3H, s), 2.66 (2H, m), 3.08 (2H, m), 3.20 (1H, d, J = 12.0 Hz), 3.31 (1H, dd, J = 4.5 Hz, 17.7 Hz), 3.45 (1H, d, J = 17.4 Hz), 3.61 (3H, s), 3.63 (1H, m), 3.77 (1H, m), 3.87 (3H, s), 4.47 (1H, d, J = 12.0 Hz), 4.63 (1H, q, J = 4.2 Hz), 6.18 (1H, s), 6.65 (1H, m), 6.98 (1H, m), 7.18 (2H, m), 7.29 (2H, m), 7.38 (3H, m), 7.80 (1H, d, J = 8.1 Hz).

Example 80

4-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahdyro-4,1-benzoxazepin-3-yl]acetyl}phenyl)butanoic acid

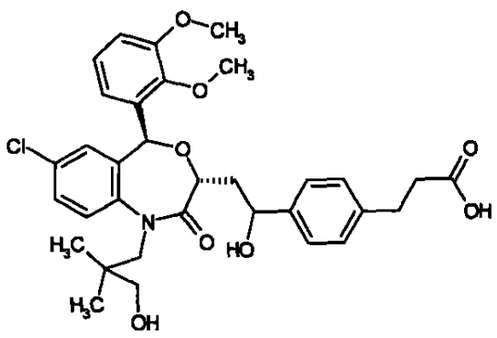


According to a similar manner to that of Example 72, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 1.96 (2H, m), 2.35 (2H, t, J = 6.9 Hz), 2.71 (2H, t, J = 7.8 Hz), 3.16 (1H, d, J = 12.0 Hz), 3.34 (1H, dd, J = 4.5 Hz, 17.4 Hz), 3.42 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.63 (1H, m), 3.81 (1H, t, J = 8.7 Hz), 3.88 (3H, s), 4.48 (1H, d, J = 14.1 Hz), 4.62 (1H, q, J = 3.9 Hz), 6.18 (1H, s), 6.62 (1H, m), 6.97 (1H, m), 7.17 (2H, m), 7.29 (2H, m), 7.39 (2H, m), 7.89 (2H, d, J = 8.1 Hz).

Example 81

3-(4-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-1-hydroxyethyl}phenyl)propionic acid



(1) Acetyl chloride (0.4 ml) was added to a solution of ethyl 3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)propionate (3.0 g) obtained in Example 72-(1) in a mixture of THF (50 ml) and pyridine (0.8 ml), and the mixture was stirred at room temperature for 2 hours. Water was added to the reaction solution, followed by extraction with ethyl acetate. The resulting organic layer was washed successively with diluted hydrochloric acid, an aqueous saturated $NaHCO_3$ solution and water, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain ethyl 3-(4-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)propionate (2.7 g) as an oil.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.02 (3H, s), 1.26 (3H, t, J = 7.2 Hz), 2.04 (3H, s), 2.62 (2H, t, J = 7.8 Hz), 2.99 (2H, t, J = 7.8 Hz), 3.30 (1H, dd, J = 4.8, 17.4 Hz), 3.60 (1H, m), 3.61 (3H, s), 3.76 (2H, m), 3.89 (3H, s),

4.11 (2H, q, J = 7.2 Hz), 4.56 (1H, d, J = 14.4 Hz), 4.62 (1H, q, J = 4.8 Hz), 6.28 (1H, s), 6.65 (1H, m), 6.97 (1H, m), 7.16 (2H, m), 7.26 (2H, m), 7.36 (2H, m), 7.89 (2H, d, J = 8.4 Hz).

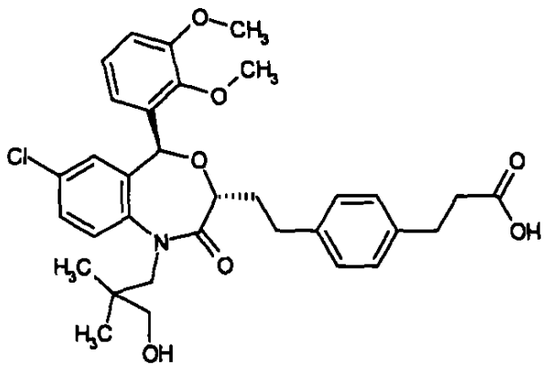
(2) Sodium borohydride (40 mg) and methanol (2 ml) were successively added to a solution of ethyl 3-(4-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)propionate (0.2 g) obtained in Example 81-(1) in THF (5 ml) and the mixture was stirred at room temperature for 30 minutes. After 1N hydrochloric acid was added, the reaction solution was extracted with ethyl acetate. The resulting organic layer was washed successively with diluted hydrochloric acid and water, dried over magnesium sulfate, and then concentrated under reduced pressure. After the resulting residue was dissolved in THF (5 ml) and ethanol (5 ml), a 2N aqueous sodium hydroxide solution (2.5 ml) was added thereto and the mixture was stirred at room temperature for 2 hours. The reaction solution was acidified with diluted hydrochloric acid and then extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain 3-(4-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-

1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-1-hydroxyethyl}phenyl)propionic acid (83 mg) as powder.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.27 (2H, m), 2.64 (2H, m), 2.93 (2H, m), 3.16 (1H, d, J = 12.0 Hz), 3.37 (1H, d, J = 14.1 Hz), 3.61 (2H, m), 3.63 (3H, s), 3.90 (3H, s), 4.14 (1H, m), 4.47 (1H, d, J = 14.1 Hz), 4.83 (1H, m), 6.18 (1H, s), 6.64 (1H, m), 7.00 (1H, m), 7.1-7.4 (8H, m).

Example 82

3-(4-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}phenyl)propionic acid



Thionyl chloride (0.2 ml) was added to a solution of ethyl 3-(4-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)propionate (1.2 g) obtained in Example 81-(1) in a mixture of dichloromethane

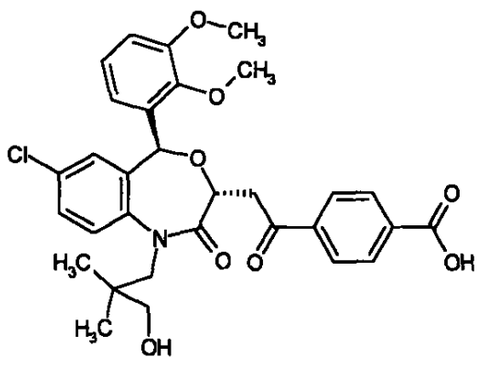
(30 ml) and pyridine (0.5 ml), and the mixture was stirred at room temperature for 1 hour. After diluted hydrochloric acid was added, the reaction solution was extracted with dichloromethane. The organic layer was washed successively with diluted hydrochloric acid, an aqueous saturated $NaHCO_3$ solution and water, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was dissolved in acetic acid (10 ml), a zinc powder (2.5 g) was added thereto, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was filtered with Celite and the filtrate was concentrated under reduced pressure. An aqueous saturated $NaHCO_3$ solution was added to the resulting residue and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography. The resulting oil was dissolved in THF (10 ml) and ethanol (10 ml), a 2N aqueous NaOH solution (5.0 ml) was added thereto, and the mixture was stirred at room temperature for 2 hours. The reaction solution was acidified with diluted hydrochloric acid and then extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain 3-(4-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-

dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}phenyl)propionic acid (115 mg) as powder.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.19 (2H, m), 2.63 (2H, m), 2.90 (2H, m), 3.15 (1H, d, J = 11.7 Hz), 3.37 (1H, d, J = 14.1 Hz), 3.62 (4H, m), 3.63 (3H, s), 3.81 (2H, m), 3.90 (3H, s), 4.45 (1H, d, J = 14.1 Hz), 6.18 (1H, s), 6.64 (1H, m), 7.00 (1H, m), 7.1-7.4 (8H, m).

Example 83

4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}benzoic acid



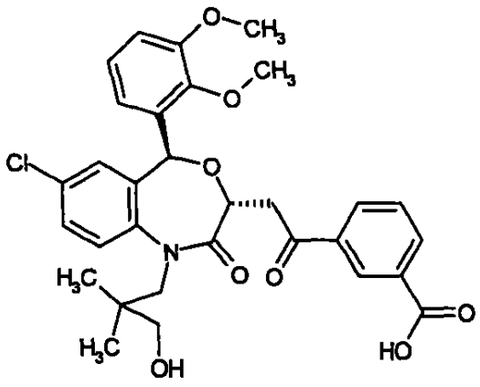
Palladium acetate (655 mg), 1,1'-bis(diphenylphosphino)ferrocene (1.6 g) and triethylamine (4.0 ml) were added to a solution of (3R,5S)-3-[2-(4-bromophenyl)-2-oxoethyl]-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-1,5-dihydro-4,1-benzoxazepin-2-(3H)-one (6.0 g) obtained in Example 71-(1) in a mixture of DMF (60 ml) and methanol (30 ml), and the

mixture was heated at 60°C for 20 hours under carbon monoxide atmosphere. After 1N hydrochloric acid was added, the reaction solution was extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the resulting oil was dissolved in a mixture of THF (100 ml) and ethanol (100 ml). Thereto a 2N aqueous NaOH solution (25 ml) was added and the mixture was stirred at room temperature for 2 hours. The reaction solution was acidified with diluted hydrochloric acid and then extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain 4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}benzoic acid (1.7 g).

^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s), 1.05 (3H, s), 3.16 (1H, d, J = 11.7 Hz), 3.39 (1H, dd, J = 3.9 Hz, 17.7 Hz), 3.43 (1H, d, J = 13.8 Hz), 3.62 (3H, s), 3.65 (1H, m), 3.85 (1H, t, J = 7.8 Hz), 3.89 (3H, s), 4.49 (1H, d, J = 14.4 Hz), 4.63 (1H, q, J = 4.5 Hz), 6.19 (1H, s), 6.63 (1H, m), 6.98 (1H, m), 7.16 (2H, m), 7.41 (2H, m), 7.04 (2H, d, J = 8.4 Hz), 8.17 (2H, d, J = 8.4 Hz).

Example 84

3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}benzoic acid

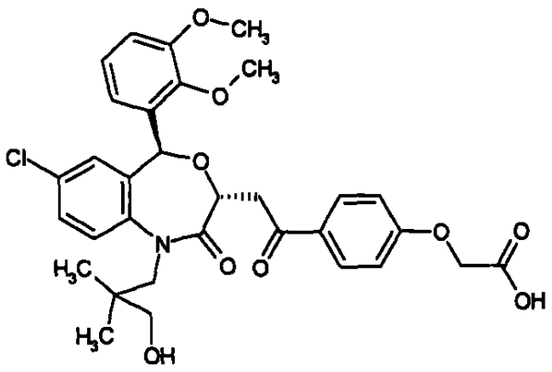


According to a similar manner to that of Example 83, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s), 1.06 (3H, s), 3.17 (1H, d, J = 11.7 Hz), 3.42 (1H, m), 3.63 (3H, s), 3.67 (1H, m), 3.90 (3H, s), 3.93 (1H, m), 4.50 (1H, d, J = 14.7 Hz), 4.66 (1H, q, J = 4.5 Hz), 6.21 (1H, s), 6.65 (1H, m), 7.00 (1H, m), 7.19 (2H, m), 7.42 (2H, m), 7.59 (1H, t, J = 7.8 Hz), 8.20 (1H, m), 8.30 (1H, m), 8.71 (1H, m).

Example 85

(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenoxy)acetic acid



(1) According to a similar manner to that of Example 71-(1), (3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-3-[2-(4-hydroxyphenyl)-2-oxoethyl]-1,5-dihydro-4,1-benzoxazepin-2(3H)-one was synthesized using (2E)-4-(acetoxyphenyl)-4-oxo-2-butenoic acid as the starting material.

^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s), 1.05 (3H, s), 3.17 (1H, m), 3.28 (1H, dd, J = 4.5 Hz, 16.8 Hz), 3.43 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.65 (1H, m), 3.79 (1H, m), 3.89 (3H, s), 4.47 (1H, d, J = 14.1 Hz), 4.62 (1H, m), 6.18 (1H, s), 6.62 (1H, m), 6.84 (2H, d, J = 8.7 Hz), 6.97 (1H, t, J = 4.5 Hz), 7.17 (2H, m), 7.39 (2H, m), 7.87 (2H, d, J = 8.7 Hz).

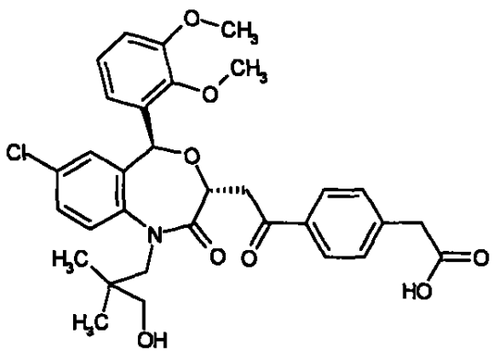
(2) K_2CO_3(0.5 g) and ethyl bromoacetate (0.22 ml) were added to a solution of (3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-3-[2-(4-hydroxyphenyl)-2-oxoethyl]-1,5-dihydro-4,1-benzoxazepin-2(3H)-one (1.0 g) obtained in Example 85-(1) in DMF (20 ml)

and the mixture was stirred at room temperature for 2 hours. After 1N hydrochloric acid was added, the reaction solution was extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. After the resulting residue was dissolved in a mixture of THF (10 ml) and ethanol (10 ml), a 2N aqueous NaOH solution (5 ml) was added thereto and the mixture was stirred at room temperature for 2 hours. The reaction solution was acidified with diluted hydrochloric acid and then extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain (4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenoxy)acetic acid (0.82 g) as powder.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 3.20 (1H, d, J = 12.0 Hz), 3.31 (1H, dd, J = 3.9 Hz, 17.1 Hz), 3.42 (1H, d, J = 15.0 Hz), 3.62 (3H, s), 3.66 (1H, m), 3.81 (1H, m), 3.90 (3H, s), 4.46 (1H, d, J = 14.7 Hz), 4.61 (1H, m), 4.71 (2H, s), 6.17 (1H, s), 6.63 (1H, m), 6.94 (2H, d, J = 9.0 Hz), 7.00 (1H, m), 7.17 (2H, m), 7.40 (2H, m), 7.95 (2H, d, J = 9.0 Hz).

Example 86

(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)acetic acid



(1) According to a similar manner to that of Example 71-(1), ethyl (4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)acetate was synthesized using (2E)-4-[4-(2-ethoxy-2-oxoethyl)phenyl]-4-oxo-2-butenoic acid as the starting material.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 1.25 (3H, t, J = 7.2 Hz), 3.14 (1H, m), 3.35 (1H, m), 3.43 (1H, d, J = 15.3 Hz), 3.65 (3H, s), 3.65 (3H, m), 3.81 (1H, m), 3.90 (3H, s), 4.15 (2H, q, J = 7.2 Hz), 4.49 (1H, d, J = 15.3 Hz), 4.63 (1H, m), 6.20 (1H, s), 6.64 (1H, m), 6.99 (1H, m), 7.18 (2H, m), 7.40 (4H, m), 7.90 (2H, m).

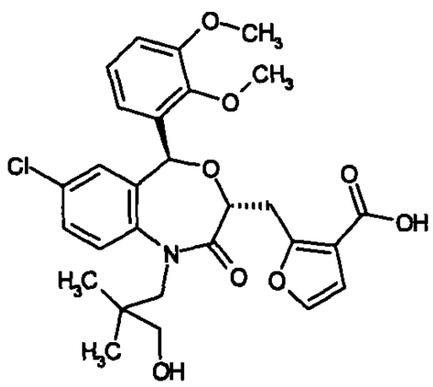
(2) A 2N aqueous NaOH solution (30 ml) was added to a solution of ethyl (4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-

1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)acetate (7.1 g) obtained in Example 86-(1) in a mixture of THF (50 ml) and ethanol (100 ml), and the mixture was stirred at room temperature for 2 hours. The reaction solution was acidified with diluted hydrochloric acid and then extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain (4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)acetic acid (4.8 g).

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 3.16 (1H, d, J = 11.7 Hz), 3.34 (1H, dd, J = 4.2 Hz, 17.4 Hz), 3.42 (1H, d, J = 14.1 Hz), 3.62 (3H, s), 3.65 (1H, m), 3.69 (2H, s), 3.81 (1H, m), 3.89 (3H, s), 4.47 (1H, d, J = 14.1 Hz), 4.62 (1H, m), 6.18 (1H, s), 6.64 (1H, m), 6.99 (1H, m), 7.17 (2H, m), 7.45 (4H, m), 7.89 (2H, m) .

Example 87

2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-3-furancarboxylic acid



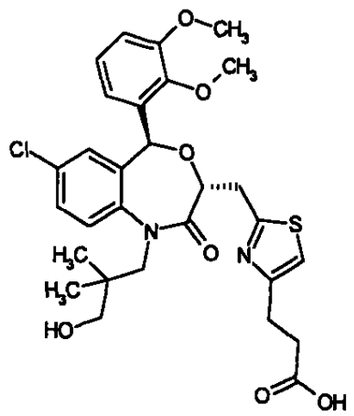
Ethyl 4-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-3-oxobutanoate (1.2 g) was dissolved in toluene (5 ml), and DBU (0.3 ml) was then added thereto. After a 40% aqueous chloroacetoaldehyde solution (0.4 ml) was then added under ice-cooling, the mixture was stirred at room temperature for 1 hour. After water was added, the reaction solution was extracted with toluene. The resulting organic layer was concentrated under reduced pressure. The resulting residue was dissolved in toluene (20 ml), a catalytic amount of p-toluenesulfonic acid was added, and the mixture was heated at 100°C for 2 hours. The reaction solution was concentrated and then purified by silica gel column. The resulting residue was dissolved in a mixture of THF (5 ml) and methanol (20 ml), a 2N aqueous NaOH solution (5 ml) was added, and the mixture was stirred at room temperature overnight. The reaction solution was acidified with diluted hydrochloric acid and then extracted

with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain 2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-3-furancarboxylic acid (26 mg).

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.06 (3H, s), 3.16 (1H, d, J = 11.7 Hz), 3.40 (1H, d, J = 14.7 Hz), 3.57 (3H, m), 3.60 (3H, s), 3.87 (3H, s), 4.29 (1H, m), 4.50 (1H, d, J = 14.7 Hz), 6.17 (1H, s), 6.53 (1H, s), 6.70 (1H, m), 6.99 (1H, d, J = 8.4 Hz), 6.95 (1H, d, J = 9.3 Hz), 7.12 (1H, t, J = 8.1 Hz), 7.31 (3H, m).

Example 88

3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-4-yl)propionic acid



(1) 10%Pd carbon (47 mg) was added to a solution of

ethyl (2E)-3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-4-yl)acrylate (0.47 g, 0.72 mmol) obtained as in Example 19-(1) in THF (5 ml) under nitrogen atmosphere, and hydrogen was then introduced. The mixture was stirred at room temperature for 48 hours and then at 40°C for 12 hours. The catalyst was filtered off using Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (73:27-65:35)] to obtain ethyl 3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-4-yl)propionate (0.38 g, 0.58 mmol, 81%) as a colorless oil.

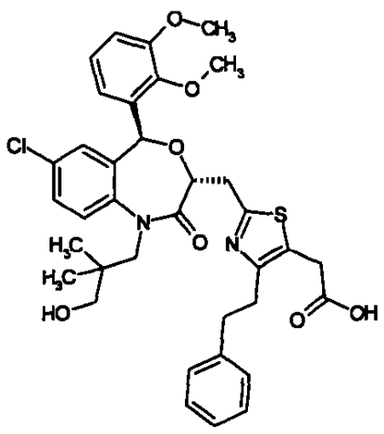
^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.03 (3H, s), 1.21 (3H, t, J = 7.2 Hz), 2.03 (3H, s), 2.67 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.45 (1H, dd, J = 7.2, 15.0 Hz), 3.54 (1H, d, J = 14.4 Hz), 3.56 (1H, dd, J = 5.7, 15.0 Hz), 3.62 (3H, s), 3.73 (1H, d, J = 11.1 Hz), 3.85 (1H, d, J = 11.1 Hz), 3.89 (3H, s), 4.11 (2H, q, J = 7.2 Hz), 4.29 (1H, dd, J = 5.7, 7.2 Hz), 4.56 (1H, d, J = 14.4 Hz), 6.31 (1H, s), 6.60 (1H, d, J = 2.4 Hz), 6.82 (1H, s), 6.98 (1H, dd, J = 2.4, 7.2 Hz), 7.10-7.20 (2H, m), 7.28 (1H, d, J = 8.4 Hz), 7.33 (1H, dd, J = 2.4, 8.4 Hz).

(2) A mixture of ethyl 3-(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-4-yl)propionate (0.35 g, 0.53 mmol) obtained in Example 88-(1), a 1N aqueous sodium hydroxide solution (3.0 ml) and ethanol (10 ml) was stirred at room temperature for 2 hours. This mixture was acidified with 1N aqueous hydrochloric acid (3.5 ml) and ethyl acetate (80 ml) was added thereto. The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain 3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-4-yl)propionic acid (0.3 g, 0.51 mmol, 96%) as colorless noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 2.69-2.80 (2H, m), 3.02 (2H, t, J = 7.2 Hz), 3.16 (1H, d, J = 12.0 Hz), 3.41 (1H, d, J = 14.7 Hz), 3.48 (1H, dd, J = 6.6, 15.3 Hz), 3.59-3.70 (2H, m), 3.62 (3H, s), 3.90 (3H, s), 4.33 (1H, t, J = 6.6 Hz), 4.47 (1H, d, J = 14.7 Hz), 6.21 (1H, s), 6.59 (1H, d, J = 2.7 Hz), 6.89 (1H, s), 7.00 (1H, dd, J = 2.4, 7.8 Hz), 7.10-7.22 (2H, m), 7.38-8.01 (2H, m).

Example 89

[2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-4-(2-phenylethyl)-1,3-thiazol-5-yl]acetic acid



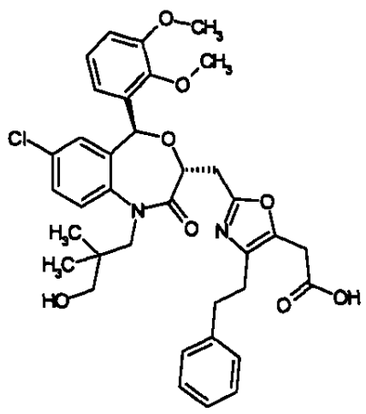
According to a similar manner to that of Example 1, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.81-2.92 (4H, m), 3.17 (1H, d, J = 11.4 Hz), 3.36 (1H, d, J = 14.4 Hz), 3.40-3.70 (3H, m), 3.46 (2H, s), 3.61 (1H, d, J = 11.7 Hz), 3.87 (3H, s), 4.34 (1H, t, J = 6.9 Hz), 4.47 (1H, d, J = 14.4 Hz), 6.20 (1H, s), 6.58 (1H, d, J = 2.4 Hz), 6.90-7.06 (3H, m), 7.09-7.38 (7H, m).

Example 90

[2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-4-(2-phenylethyl)-1,3-oxazol-5-

yl]acetic acid

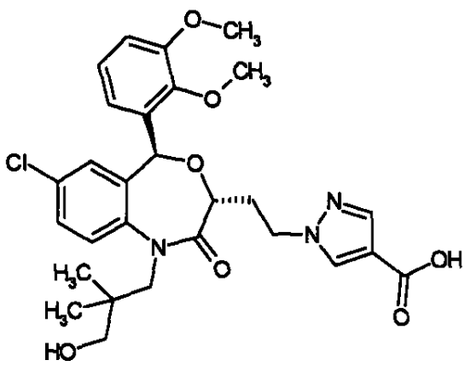


According to a similar manner to that of Example 27, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.04 (3H, s), 2.68 (2H, t, J = 7.5 Hz), 2.87 (2H, t, J = 7.5 Hz), 3.16 (1H, d, J = 12.0 Hz), 3.20-3.42 (3H, m), 3.36 (2H, s), 3.61 (3H, s), 3.62 (1H, d, J = 12.0 Hz), 3.87 (3H, s), 4.40-4.51 (2H, m), 6.18 (1H, s), 6.59 (1H, d, J = 2.1 Hz), 6.95 (1H, dd, J = 1.8, 8.1 Hz), 7.02-7.29 (8H, m), 7.37 (1H, dd, J = 2.1, 8.4 Hz).

Example 91

1-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrazole-4-carboxylic acid

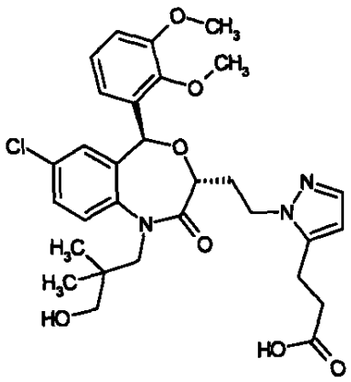


According to a similar manner to that of Example 50, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.29-2.50 (2H, m), 3.15 (1H, d, J = 12.3 Hz), 3.36 (1H, d, J = 13.8 Hz), 3.607 (1H, d, J = 12.3 Hz), 3.61 (3H, s), 3.78 (1H, t, J = 7.5 Hz), 3.89 (3H, s), 4.25-4.43 (2H, m), 4.45 (1H, d, J = 13.8 Hz), 6.15 (1H, s), 6.61 (1H, d, J = 2.4 Hz), 7.00 (1H, dd, J = 2.4, 7.2 Hz), 7.15-7.26 (2H, m), 7.28 (1H, d, J = 8.4 Hz), 7.34 (1H, dd, J = 2.4, 8.4 Hz), 7.85 (1H, s), 7.88 (1H, s).

Example 92

3-(1-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrazol-5-yl)propionic acid

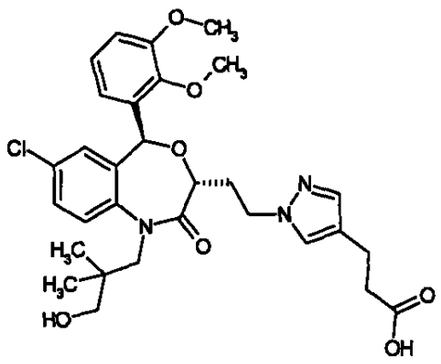


According to a similar manner to that of Example 88 using 1-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrazol-5-carboxylic acid obtained in Example 50, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 2.20-2.43 (2H, m), 2.69 (2H, t, J = 8.1 Hz), 2.87-2.98 (2H, m), 3.15 (1H, d, J = 12.3 Hz), 3.35 (1H, d, J = 14.1 Hz), 3.605 (3H, s), 3.613 (1H, d, J = 12.3 Hz), 3.88 (1H, t, J = 6.3 Hz), 3.89 (3H, s), 4.20-4.30 (2H, m), 4.41 (1H, d, J = 14.1 Hz), 5.97 (1H, d, J = 1.8 Hz), 6.13 (1H, s), 6.61 (1H, d, J = 2.1 Hz), 6.99 (1H, dd, J = 2.1, 7.8 Hz), 7.17-7.40 (5H, m).

Example 93

3-(1-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropy)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrazol-4-yl)propionic acid

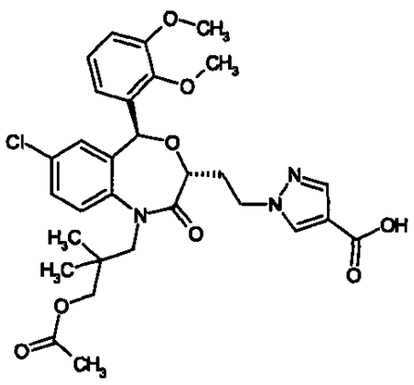


According to a similar manner to that of Example 92, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 2.23-2.40 (2H, m), 2.50 (2H, t, J = 7.2 Hz), 2.71 (2H, t, J = 7.2 Hz), 3.15 (1H, d, J = 11.7 Hz), 3.35 (1H, d, J = 14.4 Hz), 3.607 (1H, d, J = 11.7 Hz), 3.61 (3H, s), 3.72 (1H, t, J = 6.6 Hz), 3.90 (3H, s), 4.18-4.37 (2H, m), 4.42 (1H, d, J = 14.4 Hz), 6.14 (1H, s), 6.61 (1H, d, J = 2.1 Hz), 6.96-7.03 (1H, m), 7.15-7.30 (5H, m), 7.35 (1H, dd, J = 2.1, 8.7 Hz).

Example 94

1-{2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrazole-4-carboxylic acid

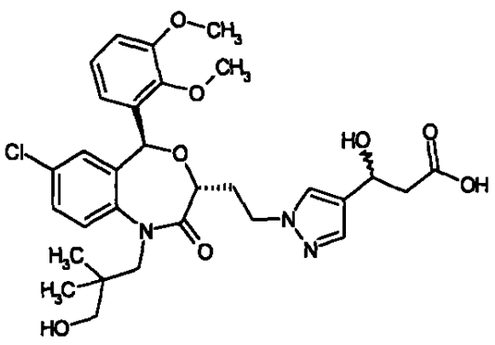


According to a similar manner to that of Example 14, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 2.03 (3H, s), 2.30-2.50 (2H, m), 3.52 (1H, d, J = 14.1 Hz), 3.62 (3H, s), 3.72 (1H, d, J = 10.8 Hz), 3.77 (1H, dd, J = 5.4, 7.2 Hz), 3.86 (1H, d, J = 10.8 Hz), 3.90 (3H, s), 4.25-4.43 (2H, m), 4.56 (1H, d, J = 14.1 Hz), 6.26 (1H, s), 6.64 (1H, d, J = 2.7 Hz), 6.97-7.05 (1H, m), 7.17-7.25 (2H, m), 7.26 (1H, d, J = 9.0 Hz), 7.33 (1H, dd, J = 2.7, 9.0 Hz), 7.86 (1H, s), 7.90 (1H, s).

Example 95

3-(1-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrazol-4-yl)-3-hydroxypropionic acid

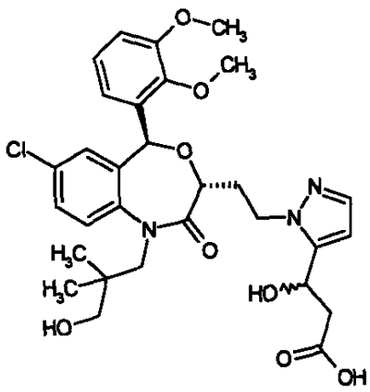


According to a similar manner to that of Example 18, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 2.28-2.40 (2H, m), 2.63-2.80 (2H, m), 3.15 (1H, d, J = 12.0 Hz), 3.35 (1H, d, J = 14.1 Hz), 3.55-3.62 (1H, m), 3.61 (3H, s), 3.76-3.82 (1H, m), 3.90 (3H, s), 4.19-4.44 (3H, m), 5.00-5.09 (1H, m), 6.13 (1H, s), 6.62 (1H, d, J = 2.1 Hz), 6.98-7.02 (1H, m), 7.19-7.22 (6H, m).

Example 96

3-(1-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrazol-5-yl)-3-hydroxypropionic acid

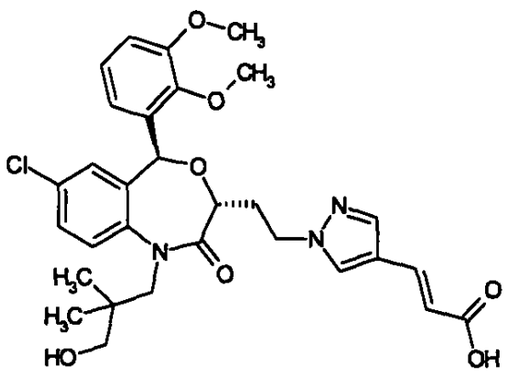


According to a similar manner to that of Example 18, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.62 (3/2H, s), 0.63 (3/2H, s), 1.02 (3/2H, s), 1.03 (3/2H, s), 2.20-2.40 (1H, m), 2.21-2.43 (1H, m), 2.79-3.03 (2H, m), 3.148 (1/2H, d, J = 12.0 Hz), 3.158 (1/2H, d, J = 12.0 Hz), 3.31 (1/2H, d, J = 14.1 Hz), 3.35 (1/2H, d, J = 14.1 Hz), 3.50-3.63 (1H, m), 3.59 (3/2H, s), 3.60 (3/2H, s), 3.88 (3H, s), 3.91-4.03 (1H, m), 4.20-4.51 (3H, m), 5.18-5.28 (1H, m), 6.09 (1/2H, s), 6.11 (1/2H, s), 6.139 (1/2H, s), 6.144 (1/sH, s), 6.61 (1H, d, J = 1.8 Hz), 6.96-7.01 (1H, m), 7.15-7.40 (5H, m).

Example 97

(2E)-3-(1-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1H-pyrazol-4-yl)acrylic acid

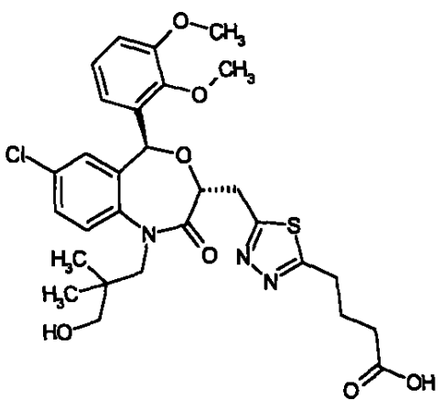


According to a similar manner to that of Example 19, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.29-2.49 (2H, m), 3.15 (1H, d, J = 12.3 Hz), 3.36 (1H, d, J = 13.5 Hz), 3.61 (1H, d, J = 12.3 Hz), 3.62 (3H, s), 3.80 (1H, dd, J = 5.4, 7.2 Hz), 3.90 (3H, s), 4.28-4.40 (2H, m), 4.46 (1H, d, J = 13.5 Hz), 6.09 (1H, d, J = 15.9 Hz), 6.16 (1H, s), 6.62 (1H, d, J = 2.4 Hz), 7.03 (1H, dd, J = 2.1, 7.2 Hz), 7.18-7.24 (2H, m), 7.29 (1H, d, J = 8.4 Hz), 7.36 (1H, dd, J = 2.4, 8.4 Hz), 7.55 (1H, s), 7.57 (1H, d, J = 15.9 Hz), 7.62 (1H, s).

Example 98

4-(5-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)-1,3,4-thiadiazol-2-yl]butanoic acid

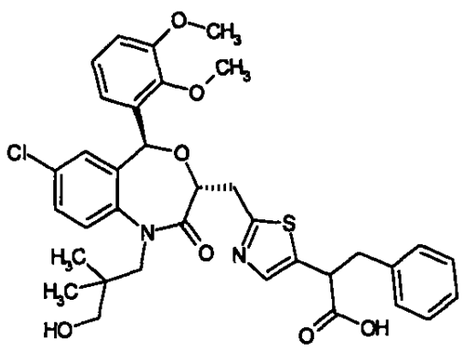


According to a similar manner to that of Example 56, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 2.15 (2H, quintet, J = 7.2 Hz), 2.49 (2H, t, J = 7.2 Hz), 3.16 (2H, t, J = 7.2 Hz), 3.10-3.20 (1H, m), 3.38 (1H, d, J = 13.8 Hz), 3.53 (1H, dd, J = 6.6, 15.3 Hz), 3.58-3.70 (2H, m), 3.62 (3H, s), 4.39 (1H, t, J = 6.6 Hz), 4.45 (1H, d, J = 13.8 Hz), 6.20 (1H, s), 6.59 (1H, d, J = 2.1 Hz), 6.99 (1H, dd, J = 1.8, 8.1 Hz), 7.12 (1H, dd, J = 1.8, 8.2 Hz), 7.19 (1H, t, J = 8.1 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.36 (1H, dd, J = 2.1, 8.4 Hz).

Example 99

2-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiadol-5-yl)-3-phenylpropionic acid



(1) Concentrated sulfuric acid (0.1 ml) was added to a solution of (2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetic acid (7.5 g, 13.0 mmol) obtained in Example 1 in ethanol (75 ml) and the mixture was heated to reflux for 24 hours with stirring. After standing to cool to room temperature, the mixture was concentrated under reduced pressure and ethyl acetate (400 ml) was added to the residue. The organic layer was washed with an aqueous saturated sodium carbonate solution, water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate and then concentrated under reduced pressure. The resulting residue was dissolved in DMF (70 ml). Imidazole (1.06 g, 15.7 mmol) and tert-butyldimethylchlorosilane (2.36 g, 15.7 mmol) were added thereto and the mixture was stirred for 14 hours. After water (50 ml) was added, the reaction solution was extracted with ethyl acetate (350 ml) and the organic layer was washed with water and an aqueous

saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (1:1)] to obtain ethyl (2-{[(3R,5S)-1-(3-{[tert-butyl(dimethyl)silyl]oxy}-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetate (7.97 g, 11.1 mmol, 85%) as pale yellow noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 0.09 (3H, s), 0.11 (3H, s), 0.96 (3H, s), 0.98 (9H, s), 1.10 (3H, s), 1.39 (3H, t, J = 6.9 Hz), 3.29 (1H, d, J = 9.9 Hz), 3.34 (1H, d, J = 9.9 Hz), 3.55 (1H, dd, J = 7.2, 15.0 Hz), 3.67 (1H, dd, J = 6.0, 15.0 Hz), 3.72 (3H, s), 3.78 (1H, d, J = 13.8 Hz), 3.89 (2H, s), 3.99 (3H, s), 4.30 (2H, q, J = 6.9 Hz), 4.43 (1H, dd, J = 6.0, 7.2 Hz), 4.50 (1H, d, J = 13.8 Hz), 6.38 (1H, s), 6.65-6.68 (1H, m), 7.07 (1H, dd, J = 2.4, 6.9 Hz), 7.20-7.31 (2H, m), 7.36-7.40 (2H, m), 7.52-7.54 (1H, m).

(2) Lithium bistrimethylsilylamide (0.63 ml, 0.7 mmol) was added dropwise to a solution of ethyl (2-{[(3R,5S)-1-(3-{[tert-butyl(dimethyl)silyl]oxy}-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetate (0.5 g, 0.70 mmol) obtained in Example 99-(1) in THF (5 ml) at -78°C under nitrogen atmosphere. After stirring at the same

temperature for 1 hour, benzyl bromide (0.08 ml, 0.7 mmol) was added dropwise thereto and the mixture was stirred at -50°C for 5 hours. After an aqueous saturated ammonium chloride solution (3 ml) was added, the mixture was extracted with ethyl acetate (60 ml), and the organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (4:1-73:27)] to obtain ethyl 2-(2-{[(3R,5S)-1-(3-{[tert-butyl(dimethyl)silyl]oxy}-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-phenylpropionate (0.33 g, 0.41 mmol, 59%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: -0.11 (3H, s), -0.02 (3H, s), 0.85 (3H, s), 0.88 (9H, s), 1.00 (3H, s), 1.15 (3/2H, t, J = 6.9 Hz), 1.16 (3/2H, t, J = 6.9 Hz), 3.05 (1/2H, dd, J = 4.8, 6.9 Hz), 3.10 (1/2H, dd, J = 4.8, 6.9 Hz), 3.19 (1H, d, J = 9.6 Hz), 3.24 (1H, d, J = 9.6 Hz), 3.32 (1/2H, dd, J = 3.3, 8.4 Hz), 3.37 (1/2H, dd, J = 3.3, 8.4 Hz), 3.44 (1H, dd, J = 7.5, 15.0 Hz), 3.53 (1H, dd, J = 5.7, 15.0 Hz), 3.62 (3H, s), 3.68 (1H, d, J = 14.1 Hz), 3.89 (3H, s), 4.02-4.16 (3H, m), 4.25-4.34 (1H, m), 4.41 (1H, d, J = 14.1 Hz), 6.28 (1H,

s), 6.57 (1H, s), 6.92-7.00 (1H, m), 7.08-7.33 (9H, m), 7.37 (1H, s).

(3) A boron trifluoride diethyl ether complex (0.16 ml, 1.22 mmol) was added dropwise to a solution of ethyl 2-(2-{[(3R,5S)-1-(3-{[tert-butyl(dimethyl)silyl]oxy}-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-phenylpropionate (0.33 g, 0.41 mmol) obtained in Example 99-(2) in acetonitrile (5 ml). After stirring at the same temperature for 1.5 hours, water (2 ml) was added thereto and the mixture was extracted with ethyl acetate (60 ml). The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (1:1-2:3)] to obtain ethyl 2-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-phenylpropionate (0.24 g, 0.35 mmol, 85%) as colorless noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.06 (3H, s), 1.16 (3H, t, J = 7.2 Hz), 3.00-3.21 (2H, m), 3.29-3.50 (3H, m), 3.55 (1H, dd, J = 5.7, 15.3 Hz), 3.59-3.70 (1H, m), 3.62 (3H, s), 3.89 (3H, s), 4.00-4.21 (4H, m), 4.27-4.39 (1H, m), 4.49

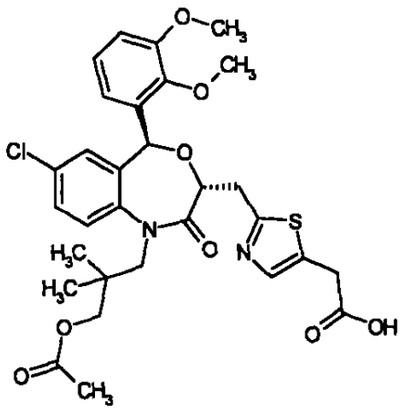
(1H, d, J = 14.4 Hz), 6.20 (1H, s), 6.57 (1H, d, J = 1.5 Hz), 6.94-7.01 (1H, m), 7.03-7.35 (9H, m), 7.37 (1H, s).

(4) A mixture of ethyl 2-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-phenylpropionate (0.2 g, 0.29 mmol) obtained in Example 99-(3), a 1N aqueous sodium hydroxide solution (1 ml) and ethanol (5 ml) was stirred at room temperature for 1 hour. The mixture was acidified with 1N aqueous hydrochloric acid (2.3 ml) and then extracted with ethyl acetate (35 ml). The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain 2-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-phenylpropionic acid (0.19 g, 0.29 mmol, quant.) as a colorless noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.04 (3/2H, s), 1.05 (3/2H, s), 3.06 (1H, dd, J = 7.5, 13.8 Hz), 3.18 (1H, d, J = 12.0 Hz), 3.37 (1H, d, J = 14.7 Hz), 3.30-3.63 (3H, m), 3.61 (3H, s), 3.63 (1H, d, J = 12.0 Hz), 3.87 (3/2H, s), 3.88 (3/2H, s), 4.05-4.17 (1H, m), 4.27-4.37 (1H, m), 4.46 (1H, d, J = 14.7 Hz), 6.19 (1H, s), 6.55-6.60 (1H, m), 6.92-7.00 (1H, m), 7.05-7.41 (10H, m).

Example 100

(2-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetic acid



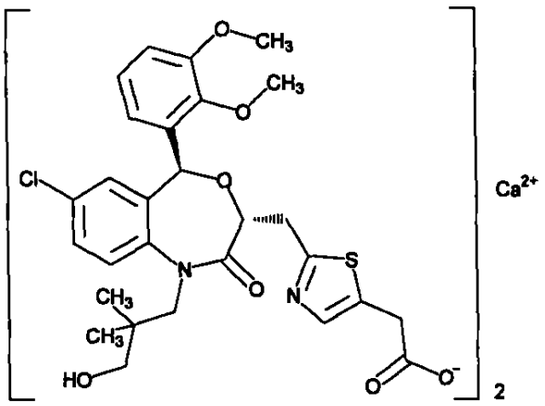
According to a similar manner to that of Example 14, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 2.02 (3H, s), 3.39-3.62 (3H, m), 3.61 (3H, s), 3.73 (1H, d, J = 10.8 Hz), 3.82 (2H, s), 3.85 (1H, d, J = 10.8 Hz), 3.88 (3H, s), 4.33 (1H, t, J = 6.9 Hz), 4.56 (1H, d, J = 13.8 Hz), 6.30 (1H, s), 6.59 (1H, d, J = 2.4 Hz), 6.96 (1H, dd, J = 3.3, 6.6 Hz), 7.10-7.20 (2H, m), 7.26-7.34 (2H, m), 7.47 (1H, s).

Example 101

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetic acid

calcium salt

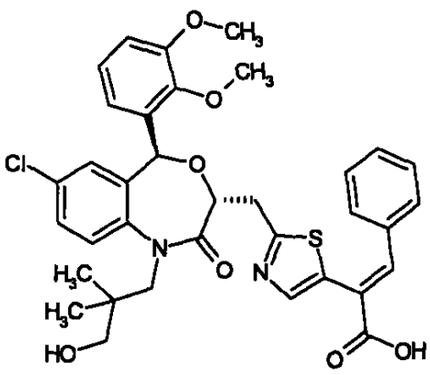


According to a similar manner to that of Example 27, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.61 (3H, s), 0.87 (3H, s), 3.04-3.30 (3H, m), 3.40-3.65 (7H, m), 3.84 (3H, s), 4.23-4.50 (2H, m), 6.13 (1H, s), 6.55 (1H, s), 6.93 (1H, d, J = 8.1 Hz), 7.09-7.38 (5H, m).

Example 102

(2Z)-2-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-phenylacrylic acid



(1) Lithium bistrimethylsilylamide (1.33 ml, 1.46 mmol) was added dropwise to a solution of ethyl (2-{[(3R,5S)-1-(3-{[tert-butyl(dimethyl)silyl]oxy}-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetate (1.0 g, 1.39 mmol) obtained in Example 99-(1) in THF (10 ml) at -78°C under nitrogen atmosphere. After stirring at the same temperature for 1 hour, benzaldehyde (0.15 g, 1.39 mmol) was added dropwise thereto and the mixture was stirred at -20°C for 5 hours. After an aqueous saturated ammonium chloride solution (5 ml) was added, the mixture was extracted with ethyl acetate (120 ml) and the organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (73:27-62:38)] to obtain ethyl 2-(2-{[(3R,5S)-1-(3-{[tert-

butyl(dimethyl)silyl]oxy}-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-hydroxy-3-phenylpropionate (0.23 g, 0.28 mmol, 20%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: -0.11 (3H, s), -0.02 (3H, s), 0.80-1.35 (9H, m), 0.87 (9H, s), 2.90-3.28 (3H, m), 3.30-3.74 (6H, m), 3.88 (3H, s), 4.00-4.43 (4H, m), 5.03-5.12 (1/2H, m), 5.17 (1/2H, m), 6.25 (1/2H, s), 6.27 (1/2H, s), 6.56 (1H, br), 6.90-7.40 (11H, m).

(2) Triethylamine (0.06 ml, 0.43 mmol) and methanesulfonyl chloride (0.03 ml, 0.43 mmol) were added to a solution of ethyl 2-(2-{[(3R,5S)-1-(3-{[tert-butyl(dimethyl)silyl]oxy}-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-hydroxy-3-phenylpropionate (0.22 g, 0.27 mmol) obtained in Example 102-(1) in THF (5 ml) under ice-cooling. After stirring at the same temperature for 1.5 hours, DBU (0.08 ml, 0.53 mmol) was added dropwise thereto and the mixture was stirred for 2 hours. After water (5 ml) was added, the reaction solution was extracted with ethyl acetate (60 ml) and the organic layer was washed with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The

resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (67:33-1:1)] to obtain ethyl (2Z)-2-(2-{[(3R,5S)-1-(3-{[tert-butyl(dimethyl)silyl]oxy}-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-phenylacrylate (0.09 g, 0.12 mmol, 44%) as colorless noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: -0.10 (3H, s), -0.01 (3H, s), 0.85 (3H, s), 0.88 (9H, s), 1.00 (3H, s), 1.33 (3H, t, J = 7.2 Hz), 3.20 (1H, d, J = 9.9 Hz), 3.24 (1H, d, J = 9.9 Hz), 3.50-3.59 (2H, m), 3.62 (3H, s), 3.69 (1H, d, J = 13.8 Hz), 3.88 (3H, s), 4.20-4.35 (3H, m), 4.42 (1H, d, J = 13.8 Hz), 6.29 (1H, s), 6.57 (1H, s), 6.95 (1H, dd, J = 2.4, 7.5 Hz), 6.99-7.11 (2H, m), 7.14-7.37 (4H, m), 7.44 (1H, s), 7.93 (1H, s).

(3) A boron trifluoride diethyl ether complex (22 µl, 0.18 mmol) was added dropwise to a solution of ethyl (2Z)-2-(2-{[(3R,5S)-1-(3-{[tert-butyl(dimethyl)silyl]oxy}-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-phenylacrylate (0.09 g, 0.12 mmol) obtained in Example 102-(2) in acetonitrile (5 ml) under ice-cooling. After stirring at the same temperature for 1.5 hours, water (2 ml) was added thereto and the mixture was extracted with

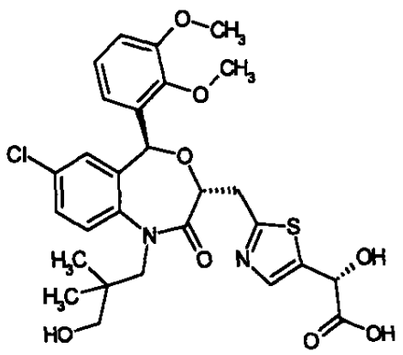
ethyl acetate (60 ml). The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was dissolved in ethanol (3 ml), a 1N aqueous sodium hydroxide solution (0.6 ml) was added, and the mixture was stirred at room temperature for 5 hours. The reaction solution was acidified with 1N aqueous hydrochloric acid (1 ml) and then extracted with ethyl acetate (35 ml). The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain (2Z)-2-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-phenylacrylic acid (0.07 g, 0.11 mmol, 85%) as pale yellow noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.06 (3H, s), 3.18 (1H, d, J = 12.0 Hz), 3.39 (1H, d, J = 14.4 Hz), 3.53-3.69 (3H, m), 3.61 (3H, s), 3.87 (3H, s), 4.37 (1H, dd, J = 5.7, 7.2 Hz), 4.49 (1H, d, J = 14.4 Hz), 6.21 (1H, s), 6.58 (1H, d, J = 1.8 Hz), 6.90-7.00 (1H, m), 7.02-7.10 (2H, m), 7.17-7.40 (7H, m), 7.51 (1H, s), 8.06 (1H, s).

Example 103

(2R)-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-

hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)(hydroxy)acetic acid

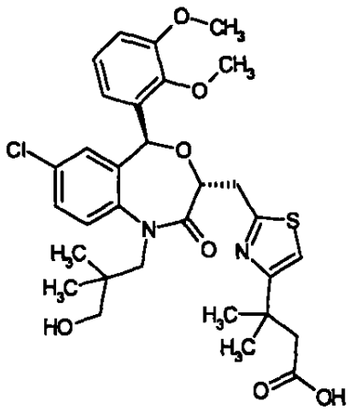


According to a similar manner to that of Example 99, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.03 (3H, s), 3.20 (1H, d, J = 12.3 Hz), 3.38 (1H, d, J = 14.1 Hz), 3.48 (1H, dd, J = 6.6, 15.3 Hz), 3.53-3.67 (2H, m), 3.60 (3H, s), 3.88 (3H, s), 4.30-4.40 (1H, m), 4.44 (1H, d, J = 14.1 Hz), 5.33 (1H, s), 6.18 (1H, s), 6.59 (1H, d, J = 1.8 Hz), 6.97 (1H, dd, J = 1.8, 7.8 Hz), 7.09-7.21 (2H, m), 7.26-7.40 (2H, m), 7.66 (1H, s).

Example 104

3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-4-yl)-3-methylbutanoic acid

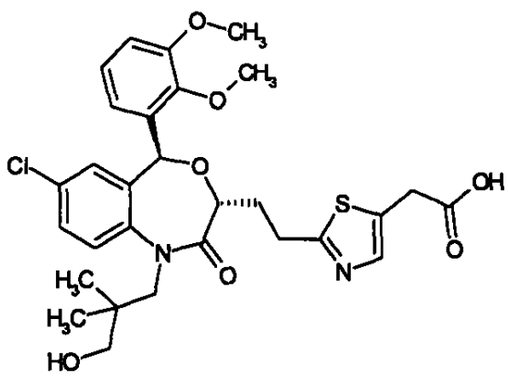


According to a similar manner to that of Example 16, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 1.39 (3H, s), 1.41 (3H, s), 2.71 (2H, s), 3.10-3.21 (1H, brs), 3.43 (1H, d, J = 14.4 Hz), 3.51 (1H, dd, J = 6.3, 15.6 Hz), 3.59-3.71 (2H, m), 3.62 (3H, s), 3.89 (3H, s), 4.32 (1H, t, J = 6.3 Hz), 4.46 (1H, d, J = 14.4 Hz), 6.21 (1H, s), 6.60 (1H, d, J = 1.8 Hz), 6.92 (1H, s), 6.99 (1H, dd, J = 2.7, 7.5 Hz), 7.10-7.20 (2H, m), 7.35-7.45 (2H, m).

Example 105

(2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1,3-thiazol-5-yl)acetic acid



(1) To a solution of (3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-ethanol (1.0 g, 1.98 mmol) obtained in Example 50-(1), acetone cyanohydrin (0.23 ml, 2.57 mmol) and toluene (20 ml) were added n-tributylphosphine (0.74 ml, 2.96 mmol) and 1,1'-azodicarbonyldipiperidine (0.75 g, 2.96 mmol) under nitrogen atmosphere, and the mixture was stirred at room temperature for 3 hours. After hexane (10 ml) was added, the mixture was stirred for 30 minutes and then filtered to remove insoluble substances. The filtrate was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (7:3-3:2)] to obtain 3-[(3R,5S)-7-chloro-3-(2-cyanoethyl)-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (0.75 g, 1.46 mmol, 74%) as colorless noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 2.03 (3H, s), 2.00-2.35 (2H, m), 2.57 (2H, t, J = 7.5 Hz), 3.53 (1H, d, J = 14.4 Hz), 3.62 (3H, s), 3.72 (1H, d, J = 11.1 Hz), 3.86 (1H, d, J = 11.1 Hz), 3.90 (3H, s), 3.99 (1H, dd, J = 4.8, 7.5 Hz), 4.57 (1H, d, J = 14.4 Hz), 6.27 (1H, s), 6.66 (1H, d, J = 2.1 Hz), 7.00 (1H, dd, J = 3.0, 7.2 Hz), 7.16-7.25 (2H, m), 7.30 (1H, d, J = 8.7 Hz), 7.36 (1H, dd, J = 2.1, 8.7 Hz).

(2) O,O'-diethyl dithiophosphate (0.20 ml, 1.17 mmol) was added to a solution of 3-[(3R,5S)-7-chloro-3-(2-cyanoethyl)-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (0.5 g, 0.97 mmol) obtained in Example 105-(1) and 4N HCl (2.5 ml), and the mixture was stirred at room temperature for 16 hours. After water (5 ml) was added, the mixture was extracted with ethyl acetate and the organic layer was washed with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (3:2-1:1)] to obtain 3-[(3R,5S)-3-(3-amino-3-thioxopropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (0.38 g, 0.69 mmol, 71%) as a pale yellow crystal.

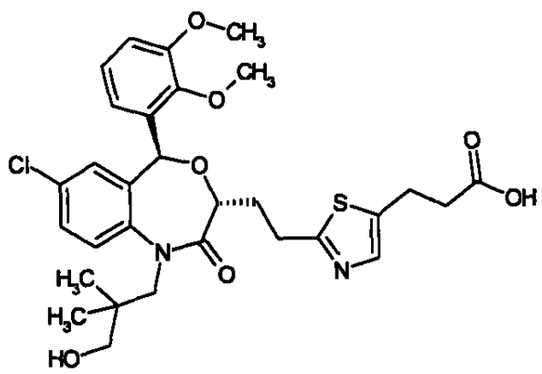
^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.01 (3H, s), 2.03 (3H, s), 2.20-2.34 (2H, m), 2.71-2.94 (2H, m), 3.52 (1H, d, J = 14.1 Hz), 3.62 (3H, s), 3.72 (1H, d, J = 11.1 Hz), 3.88 (1H, d, J = 11.1 Hz), 3.90 (3H, s), 3.96 (1H, t, J = 6.3 Hz), 4.56 (1H, d, J = 14.1 Hz), 6.26 (1H, s), 6.64 (1H, d, J = 2.4 Hz), 6.95-7.04 (1H, m), 7.15-7.24 (2H, m), 7.29 (1H, d, J = 9.0 Hz), 7.35 (1H, dd, J = 2.4, 9.0 Hz), 7.30-7.40 (1H, m), 7.48 (1H, br).

(3) According to the similar manner as that of Example 16 using 3-[(3R,5S)-3-(3-amino-3-thioxopropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate obtained in Example 105-(2), the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.04 (3H, s), 2.18-2.42 (2H, m), 2.95-3.20 (3H, m), 3.37 (1H, d, J = 14.4 Hz), 3.57-3.70 (1H, m), 3.61 (3H, s), 3.74 (2H, s), 3.82-3.99 (1H, m), 3.89 (3H, s), 4.46 (1H, d, J = 14.4 Hz), 6.15 (1H, s), 6.59 (1H, s), 6.92-7.02 (1H, m), 7.13-7.23 (2H, m), 7.25-7.40 (3H, m).

Example 106

3-(2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1,3-tihazol-5-yl)propionic acid

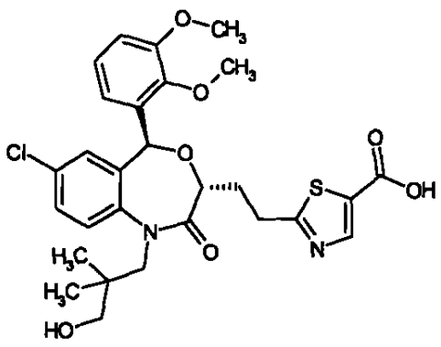


According to a similar manner to that of Example 105, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.04 (3H, s), 2.17-2.41 (2H, m), 2.62 (2H, t, J = 7.2 Hz), 2.95-3.21 (5H, m), 3.36 (1H, d, J = 14.4 Hz), 3.607 (3H, s), 3.612 (1H, d, J = 11.7 Hz), 3.88 (3H, s), 3.84-3.94 (1H, m), 4.44 (1H, d, J = 14.4 Hz), 6.14 (1H, s), 6.60 (1H, d, J = 1.8 Hz), 6.98 (1H, dd, J = 2.4, 6.9 Hz), 7.13-7.22 (2H, m), 7.26 -7.40 (3H, m).

Example 107

2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1,3-thiazol-5-carboxylic acid

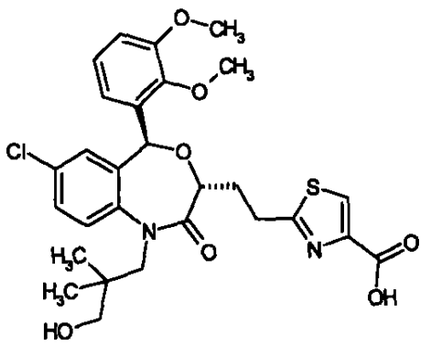


According to a similar manner to that of Example 105, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.06 (3H, s), 2.20-2.50 (2H, m), 3.08-3.32 (2H, m), 3.17 (1H, d, J = 11.4 Hz), 3.37 (1H, d, J = 14.4 Hz), 3.62 (3H, s), 3.63 (1H, d, J = 11.4 Hz), 3.89 (3H, s), 3.95 (1H, dd, J = 5.1, 7.5 Hz), 4.48 (1H, d, J = 14.4 Hz), 6.16 (1H, s), 6.61 (1H, d, J = 2.1 Hz), 6.99 (1H, dd, J = 3.0, 6.6 Hz), 7.13-7.23 (2H, m), 7.29 (1H, d, J = 8.7 Hz), 7.35 (1H, dd, J = 2.1, 8.7 Hz), 8.27 (1H, s).

Example 108

2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1,3-tihazol-4-carboxylic acid

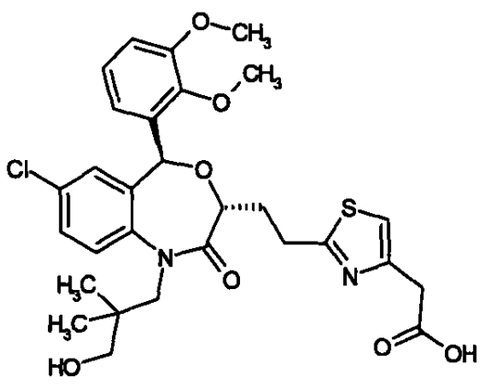


According to a similar manner to that of Example 105, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.22-2.50 (2H, m), 3.06-3.38 (2H, m), 3.17 (1H, d, J = 11.4 Hz), 3.37 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.62 (1H, d, J = 11.4 Hz), 3.89 (3H, s), 3.95 (1H, dd, J = 5.4, 7.5 Hz), 4.46 (1H, d, J = 14.1 Hz), 6.15 (1H, s), 6.60 (1H, d, J = 2.1 Hz), 6.99 (1H, dd, J = 2.4, 7.5 Hz), 7.10-7.23 (2H, m), 7.31 (1H, d, J = 8.4 Hz), 7.36 (1H, dd, J = 2.1, 8.4 Hz), 8.10 (1H, s) .

Example 109

(2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1,3-thiazol-4-yl)acetic acid

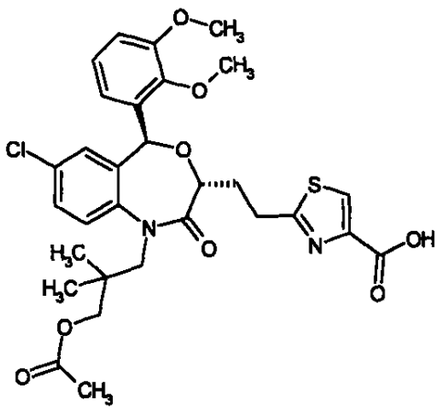


According to a similar manner to that of Example 105, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.18-2.45 (2H, m), 3.03-3.30 (3H, m), 3.38 (1H, d, J = 14.4 Hz), 3.617 (3H, s), 3.618 (1H, d, J = 11.7 Hz), 3.77 (2H, d, J = 1.2 Hz), 3.89 (3H, s), 3.93 (1H, dd, J = 5.4, 7.5 Hz), 4.47 (1H, d, J = 14.4 Hz), 6.16 (1H, s), 6.61 (1H, d, J = 2.1 Hz), 6.95 (1H, t, J = 1.2 Hz), 6.95-7.01 (1H, m), 7.16-7.23 (2H, m), 7.31 (1H, d, J = 8.4 Hz), 7.36 (1H, dd, J = 2.1, 8.4 Hz).

Example 110

2-{2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1,3-thiazol-5-carboxylic acid

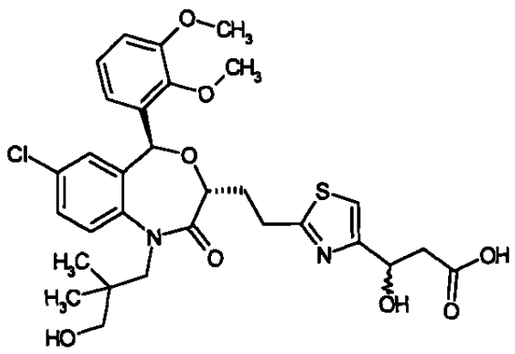


According to a similar manner to that of Example 14, the title compound was obtained.

^{1}H-NMR (CD_3OD) δ: 0.98 (3H, s), 0.99 (3H, s), 1.98 (3H, s), 1.90-2.23 (2H, m), 2.90-3.20 (2H, m), 3.58 (3H, s), 3.60-3.92 (3H, m), 3.87 (3H, s), 4.45 (1H, d, J = 14.1 Hz), 4.75-4.90 (1H, m), 6.20 (1H, s), 6.51 (1H, d, J = 2.1 Hz), 6.99-7.21 (3H, m), 7.35-7.45 (1H, m), 7.54 (1H, d, J = 9.0 Hz), 7.90 (1H, s).

Example 111

3-(2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1,3-thiazole-4-yl)-3-hydroxypropionic acid

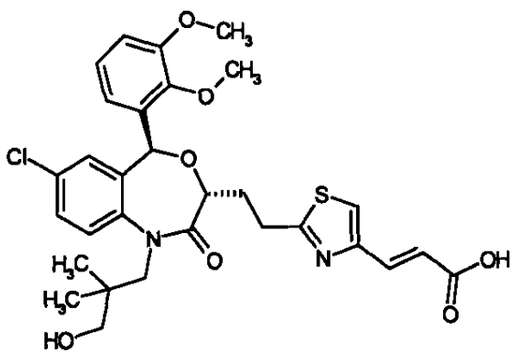


According to a similar manner to that of Example 18, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.18-2.42 (2H, m), 2.73-2.82 (1H, m), 2.82-2.96 (2H, m), 3.00-3.22 (2H, m), 3.15 (1H, d, J = 12.0 Hz), 3.37 (1H, d, J = 13.8 Hz), 3.61 (3H, s), 3.62 (1H, d, J = 12.0 Hz), 3.89 (3H, s), 3.90-4.01 (1H, m), 4.47 (1H, d, J = 13.8 Hz), 5.10-5.17 (1H, m), 6.15 (1H, s), 6.60 (1H, d, J = 2.1 Hz), 6.95-7.01 (1H, m), 7.07 (1H, s), 7.15-7.21 (2H, m), 7.31 (1H, d, J = 8.7 Hz), 7.36 (1H, dd, J = 2.1, 8.7 Hz).

Example 112

(2E)-3-(2-{2-[3R,5S]-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl}ethyl)-1,3-thiazol-4-yl)acrylic acid

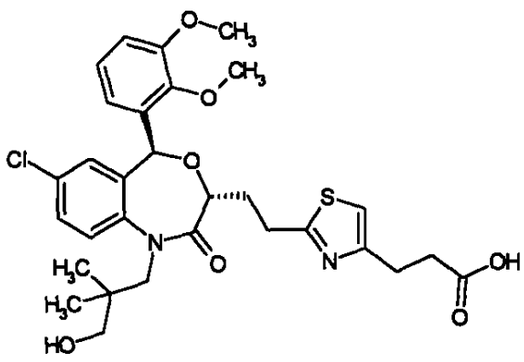


According to a similar manner to that of Example 19, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.06 (3H, s), 2.20-2.43 (2H, m), 3.05-3.24 (3H, m), 3.38 (1H, d, J = 14.4 Hz), 3.62 (3H, s), 3.60-3.69 (1H, m), 4.05 (1H, dd, J = 5.7, 7.2 Hz), 4.47 (1H, d, J = 14.4 Hz), 6.16 (1H, s), 6.59 (1H, d, J = 15.3 Hz), 6.60 (1H, d, J = 2.4 Hz), 6.98 (1H, dd, J = 2.7, 6.6 Hz), 7.14-7.29 (3H, m), 7.32 (1H, d, J = 8.7 Hz), 7.37 (1H, dd, J = 2.4, 8.4 Hz), 7.58 (1H, d, J = 15.3 Hz).

Example 113

3-(2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1,3-thiazol-4-yl)propionic acid

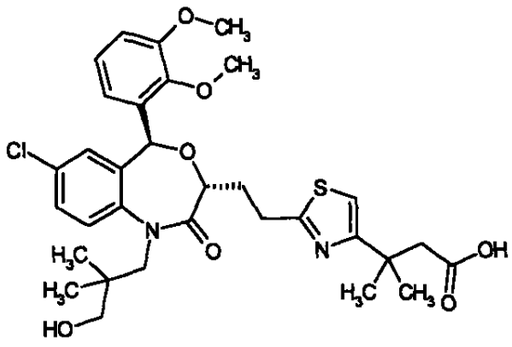


According to a similar manner to that of Example 88, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.20-2.42 (2H, m), 2.60-2.75 (2H, m), 2.90-3.25 (3H, m), 3.38 (1H, d, J = 14.7 Hz), 3.619 (3H, s), 3.624 (1H, d, J = 11.7 Hz), 3.89 (3H, s), 3.96 (1H, dd, J = 5.4, 6.9 Hz), 4.48 (1H, d, J = 14.7 Hz), 6.16 (1H, s), 6.61 (1H, d, J = 1.8 Hz), 6.80 (1H, s), 6.96-7.03 (1H, m), 7.17-7.23 (2H, m), 7.27-7.40 (2H, m).

Example 114

3-(2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1,3-thiazol-4-yl)-3-methylbutanoic acid

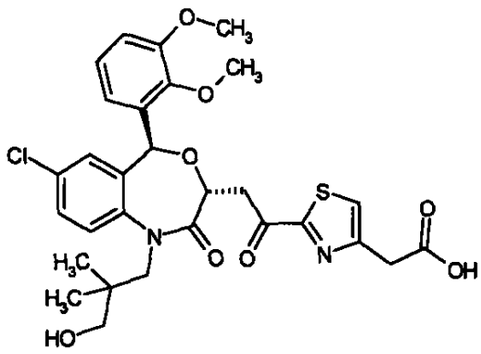


According to a similar manner to that of Example 16, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.06 (3H, s), 1.38 (3H, s), 1.39 (3H, s), 2.20-2.42 (2H, m), 2.67 (1H, d, J = 15.0 Hz), 3.10-3.35 (3H, m), 3.41 (1H, d, J = 14.7 Hz), 3.62 (3H, s), 3.63 (1H, d, J = 11.7 Hz), 3.90 (3H, s), 3.96 (1H, t, J = 5.7Hz), 4.48 (1H, d, J = 14.7 Hz), 6.16 (1H, s), 6.61 (1H, s), 6.90 (1H, s), 7.00 (1H, dd, J = 2.1, 7.8 Hz), 7.14-7.22 (2H, m), 7.30-7.40 (2H, m).

Example 115

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}-1,3-thiazol-4-yl)acetic acid



(1) A solution of a sulfur trioxide pyridine complex (5.76 g, 36.2 mmol) in DMSO (18 ml) was added dropwise to a solution of (3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-ethanol (3.66 g, 7.23 mmol) obtained in Example 50-(1) in dichloromethane (70 ml). After stirring at room temperature for 1.5 hours, water (15 ml) was added. After extraction with dichloromethane (150 ml), the organic layer was washed with a 5% aqueous potassium hydrogen sulfate solution, an aqueous saturated sodium hydrogen carbonate solution, water and an aqueous saturated sodium chloride solution, and then dried over magnesium sulfate. After concentration under reduced pressure, the resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (2:1)] and then washed with 2-propanol-hexane to obtain 3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-3-(2-oxoethyl)-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (2.39 g, 4.74 mmol, 66%) as a white crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 2.03 (3H, s), 2.86 (1H, ddd, J = 1.2, 5.4, 17.7 Hz), 3.09 (1H, ddd, J = 1.2, 6.9, 17.7 Hz), 3.55 (1H, d, J = 14.4 Hz), 3.62 (3H, s), 3.73 (1H, d, J = 11.1 Hz), 3.86 (1H, d, J = 11.1 Hz), 3.89 (3H, s), 4.42 (1H, dd, J = 5.4, 6.9 Hz), 4.56 (1H, d, J = 14.1 Hz), 6.28 (1H, s), 6.66 (1H, d, J = 1.8 Hz), 6.96-7.01 (1H, m), 7.15-7.23 (2H, m), 7.28-7.40 (2H, m), 9.81 (1H, br).

(2) A solution of 3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-3-(2-oxoethyl)-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (2.0 g, 3.97 mmol) obtained in Example 115-(1) in dichloromethane (25 ml) was added dropwise to a solution of tert-butyldimethylsilyl cyanide (0.59 g, 4.17 mmol), potassium cyanide (44 mg, 0.68 mmol) and 18-crown-6-ether (0.42 g, 1.59 mmol) in dichloromethane (25 ml) under nitrogen atmosphere. The mixture was stirred at room temperature for 18 hours and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (41:9-3:1)] to obtain 3-[(3R,5S)-3-(2-{[tert-butyl(dimethyl)silyl]oxy}-2-cyanoethyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (1.96 g, 3.04 mmol, 77%) as a white crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.04 (3H. s), 0.14 (3/2H, s), 0.15 (3/2H, s), 0.68 (9/2H, s), 0.79 (9/2H, s), 0.95 (3/2H, s), 0.96 (3/2H, s), 2.03 (3H, s), 2.18-2.45 (2H, m), 3.52 (1H, d, J = 14.1 Hz), 3.62 (3H, s), 3.73 (1/2H, d, J = 11.1 Hz), 3.74 (1/2H, d, J = 11.1 Hz), 3.98-4.16 (1H, m), 4.55 (1/2H, d, J = 14.1 Hz), 4.56 (1/2H, d, J = 14.1 Hz), 4.61-4.76 (1H, m), 6.26 (1H, s), 6.99 (1/2H, d, J = 2.7 Hz), 7.01 (1/2H, d, J = 2.7 Hz), 6.95-7.02 (1H, m), 7.10-7.39 (4H, m).

(3) Diphenyldithiophosphoric acid (0.39 g, 1.55 mmol) was added to a solution of 3-[(3R,5S)-3-(2-{[tert-butyl(dimethyl)silyl]oxy}-2-cyanoethyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (0.5 g, 0.78 mmol) obtained in Example 115-(2) in isopropyl alcohol (10 ml), and the mixture was stirred at 60°C for 14 hours. The mixture was cooled to room temperature and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (41:9-3:1)] to obtain 3-[(3R,5S)-3-(3-amino-2-{[tert-butyl(dimethyl)silyl]oxy}-3-thioxopropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (0.48 g, 0.71 mmol, 91%) as a white crystal.

^{1}H-NMR ($CDCl_3$) δ: -0.06 (3/2H. s), -0.02 (3/2H, s), 0.03 (3/2H, s), 0.04 (3/2H, s), 0.76 (9/2H, s), 0.81 (9/2H,

s), 0.94 (3/2H, s), 0.95 (3/2H, s), 1.03 (3H, s), 2.03 (3H, s), 2.01-2.20 (1H, m), 2.39-2.60 (1H, m), 3.51 (1/2H, d, J = 14.1 Hz), 3.52 (1/2H, d, J = 14.1 Hz), 3.60 (3H, s), 3.69-3.78 (1H, m), 3.84 (1/2H, d, J = 10.8 Hz), 3.85 (1/2H, d, J = 10.8 Hz), 3.89 (3H, s), 4.08 (1/2H, dd, J = 6.0, 10.5 Hz), 4.29 (1/2H, t, J = 6.6 Hz), 4.54 (1/2H, d, J = 14.1 Hz), 4.56 (1/2H, d, J = 14.1 Hz), 4.63 (1/2H, t, J = 6.6 Hz), 4.72 (1/2H, dd, J = 4.5, 9.0 Hz), 6.25 (1H, s), 6.60-6.67 (1H, m), 6.95-7.01 (1H, m), 7.14-7.43 (5H, m), 7.72-7.82 (1H, m).

(4) A solution of 3-[(3R,5S)-3-(3-amino-2-{[tert-butyl(dimethyl)silyl]oxy}-3-thioxopropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (0.42 g, 0.62 mmol) obtained in Example 115-(3) and ethyl 4-chloro-3-oxobutanoate (84 µl, 0.62 mmol) in ethanol (10 ml) was stirred at 80°C for 32 hours. After standing to cool, water (5 ml) was added thereto and the mixture was extracted with ethyl acetate (130 ml). The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (41:9-3:1)] to obtain ethyl (2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-

1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-1-hydroxyethyl}-1,3-thiazol-4-yl)acetate (0.18 g, 0.28 mmol, 45%) as a white crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 1.26 (3H, t, J = 7.2 Hz), 2.25-2.48 (1H, m), 2.50-2.70 (1H, m), 3.15 (1H, t, J = 11.1 Hz), 3.38 (1H, d, J = 14.4 Hz), 3.54-3.70 (1H, m), 3.62 (3/2H, s), 3.64 (3/2H, s), 3.74 (1H, s), 3.75 (1H, s), 3.89 (3H, s), 3.99 (1/2H, dd, J = 4.2, 11.1 Hz), 4.07 (1/2H, dd, J = 4.2, 11.1 Hz), 4.10-4.30 (3H, m), 4.47 (1/2H, d, J = 14.4 Hz), 4.50 (1/2H, d, J = 14.4 Hz), 5.11-5.23 (1H, m), 6.18 (1/2H, s), 6.19 (1/2H, s), 6.61 (1/2H, d, J = 2.1 Hz), 6.63 (1/2H, d, J = 2.1 Hz), 6.94-7.02 (1H, m), 7.095 (1/2H, s), 7.103 (1/2H, s), 7.14-7.40 (4H, m).

(5) Manganese dioxide (0.2 g, 2.38 mmol) was added to a solution of ethyl (2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-1-hydroxyethyl}-1,3-thiazol-4-yl)acetate (0.15 g, 0.24 mmol) obtained in Example 115-(4) in THF (5 ml), and the mixture was stirred at 70°C for 4 days. After standing to cool, insoluble substances were filtered off using Celite and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (3:1-2:1)] to obtain ethyl (2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-

1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}-1,3-thiazol-4-yl)acetate (71 mg, 0.11 mmol, 48%) as a white crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 1.29 (3H, t, J = 6.9 Hz), 3.14 (1H, t, J = 10.5 Hz), 3.41 (1H, d, J = 14.4 Hz), 3.58 (1H, dd, J = 4.8, 18.3 Hz), 3.56-3.69 (1H, m), 3.62 (3H, s), 3.89 (3H, s), 3.98 (1H, dd, J = 8.1, 18.3 Hz), 4.15 (1H, dd, J = 3.9, 10.8 Hz), 4.20 (2H, q, J = 6.9 Hz), 4.49 (1H, d, J = 14.4 Hz), 4.60 (1H, dd, J = 4.8, 8.1 Hz), 6.18 (1H, s), 6.63 (1H, s), 6.95-7.01 (1H, m), 7.15-7.22 (2H, m), 7.36-7.43 (2H, m), 7.57 (1H, s).

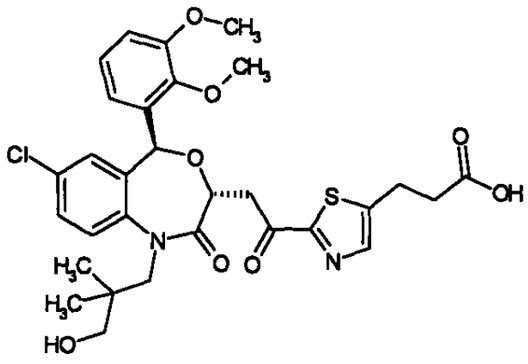
(6) A solution of ethyl (2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}-1,3-thiazol-4-yl)acetate (60 mg, 0.10 mmol) obtained in Example 115-(5) and potassium carbonate (26 mg, 0.20 mmol) in ethanol (3 ml) and water (0.5 ml) was heated to reflux for 5 hours with stirring. After standing to cool, the mixture was acidified with 1N aqueous hydrochloric acid (1 ml) and extracted with ethyl acetate (70 ml). The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting crystal was washed with ethyl acetate-hexane and then dried under reduced pressure to obtain (2-{[(3R,5S)-7-chloro-5-(2,3-

dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}-1,3-thiazol-4-yl)acetic acid (40 mg, 0.07 mmol, 70%) as a pale yellow crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 3.16 (1H, d, J = 12.0 Hz), 3.41 (1H, d, J = 14.1 Hz), 3.54 (1H, dd, J = 4.8, 18.3 Hz), 3.61 (3H, s), 3.62 (1H, d, J = 12.0 Hz), 3.88 (3H, s), 3.99 (1H, dd, J = 8.4, 18.3 Hz), 4.47 (1H, d, J = 14.1 Hz), 4.60 (1H, dd, J = 4.8, 8.4 Hz), 6.16 (1H, s), 6.62 (1H, d, J = 2.7 Hz), 6.93-7.00 (1H, m), 7.10-7.20 (2H, m), 7.33-7.42 (2H, m), 7.55 (1H, s).

Example 116

3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}-1,3-thiazol-5-yl)propionic acid



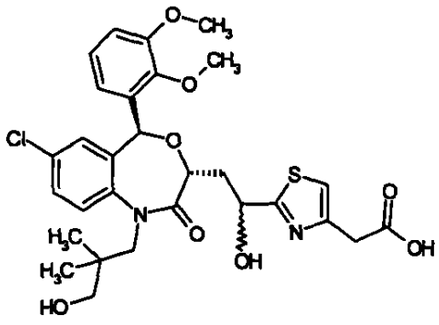
According to a similar manner to that of Example 115, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 2.76 (2H,

t, J = 7.2 Hz), 3.14 (1H, d, J = 12.0 Hz), 3.23 (1H, t, J = 7.2 Hz), 3.41 (1H, d, J = 15.0 Hz), 3.54 (1H, dd, J = 4.8, 18.0 Hz), 3.61 (3H, s), 3.62 (1H, d, J = 12.0 Hz), 3.89 (3H, s), 3.95 (1H, dd, J = 8.4, 18.0 Hz), 4.48 (1H, d, J = 15.0 Hz), 4.58 (1H, dd, J = 4.8, 8.4 Hz), 6.17 (1H, s), 6.62 (1H, s), 6.95-7.01 (1H, m), 7.13-7.20 (2H, m), 7.38-7.42 (2H, m), 7.74 (1H, s).

Example 117

(2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-1-hydroxyethyl}-1,3-thiazol-4-yl)acetic acid



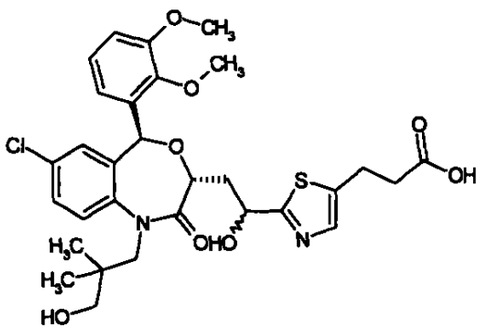
A mixture of ethyl (2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-1-hydroxyethyl}-1,3-thiazol-4-yl)acetate (0.25 g, 0.40 mmol) obtained in Example 115-(4), a 1N aqueous sodium hydroxide solution (1 ml) and ethanol (5 ml) was stirred at room temperature for

2 hours. This mixture was acidified with 1N aqueous hydrochloric acid (1.2 ml) and then extracted with ethyl acetate (35 ml). This extract was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain (2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-1-hydroxyethyl}-1,3-thiazol-4-yl)acetic acid (0.24 g, 0.40 mmol, quant.) as colorless noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s), 1.05 (3H, s), 2.30-2.70 (2H, m), 3.17 (1H, t, J = 11.7 Hz), 3.40 (1H, d, J = 14.4 Hz), 3.61 (1H, d, J = 11.7 Hz), 3.63 (3H, s), 3.79 (2H, s), 3.90 (3H, s), 4.19-4.32 (1H, m), 4.48 (1/3H, d, J = 14.4 Hz), 4.50 (2/3H, d, J = 14.4 Hz), 5.20-5.30 (1H, m), 6.18 (2/3H, s), 6.21 (1/3H, s), 6.62 (2/3H, d, J = 2.4 Hz), 6.67 (1/3H, d, J = 2.4 Hz), 6.98-7.03 (1H, m), 7.07 (1H, s), 7.15-7.23 (2H, m), 7.30-7.42 (2H, m).

Example 118

3-(2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-1-hydroxyethyl}-1,3-thiazol-5-yl)propionic acid

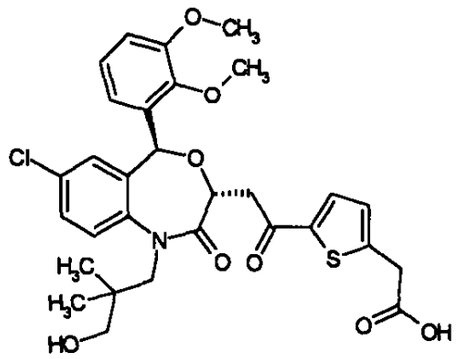


According to a similar manner to that of Example 117, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s), 1.04 (3H, s), 2.13-2.41 (2H, m), 2.50-2.60 (1H, m), 2.61 (2H, t, J = 7.5 Hz), 3.10 (2H, t, J = 7.5 Hz), 3.10-3.10 (1H, m), 3.39 (1/2H, d, J = 13.8 Hz), 3.40 (1/2H, d, J = 13.8 Hz), 3.57-3.64 (1H, m), 3.62 (3H, s), 3.90 (3H, s), 4.19-4.30 (1H, m), 4.466 (1/2H, d, J = 13.8 Hz), 4.474 (1/2H, d, J = 13.8 Hz), 5.01-5.20 (1H, m), 6.17 (1/2H, s), 6.19 (1/2H, s), 6.58-6.63 (1H, m), 6.95-7.02 (1H, m), 7.15-7.30 (2H, m), 7.31-7.43 (3H, m).

Example 119

(5-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}-2-thienyl)acetic acid



DMF (1 drop) and thionyl chloride (0.42 ml, 5.77 mmol) were added dropwise to a solution of 2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetic acid (2.5 g, 4.81 mmol) in THF (25 ml) at room temperature. The mixture was stirred for 4 hours and then concentrated under reduced pressure. The resulting residue was dissolved in dichloromethane (30 ml). Ethyl 2-thiopheneacetate (0.69 ml, 4.57 mmol) and tin chloride (1.24 ml, 10.6 mmol) were added dropwise under ice-cooling thereto. The mixture was warmed to room temperature and stirred for 13 hours. The reaction solution was poured into ice-water and extracted with dichloromethane (170 ml). The organic layer was washed with 1N aqueous hydrochloric acid, water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was subjected to silica gel column chromatography [developing solvent: hexane-ethyl acetate (1:1-3:7)] to

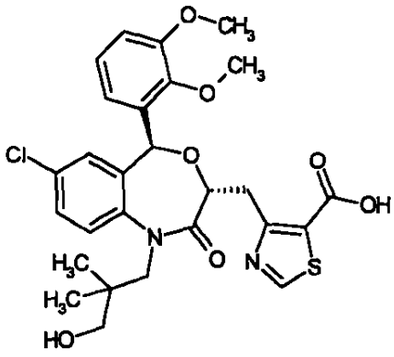
obtain ethyl (5-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}-2-thienyl)acetate as a mixture with impurities. This mixture was dissolved in ethanol (7 ml) and water (1 ml), potassium carbonate (86 mg, 0.63 mmol) was added thereto, and the mixture was then heated to reflux for 2 hours with stirring. After standing to cool, the mixture was acidified with 1N aqueous hydrochloric acid (1.5 ml) and then extracted with ethyl acetate (35 ml). The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by preparative liquid chromatography [developing solvent: water-acetonitrile (9:1-5:95)] to obtain (5-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}-2-thienyl)acetic acid (52 mg, 0.09 mmol, 2% (2 step)) as pale yellow noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.04(3H, s), 3.19 (1H, d, J = 11.7 Hz), 3.28 (1H, dd, J = 4.5, 16.8 Hz), 3.41 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.64 (1H, d, J = 11.7 Hz), 3.70 (1H, dd, J = 8.1, 16.8 Hz), 3.89 (5H, s), 4.45 (1H, d, J = 14.1 Hz), 4.58 (1H, dd, J = 4.5, 8.1 Hz), 6.17 (1H, s), 6.62 (1H, s), 6.95-7.10 (2H, m), 7.11-7.20 (2H, m), 7.35-

7.41 (2H, m), 7.66 (1H, d, J = 3.6 Hz).

Example 120

4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-tihazol-5-carboxylic acid



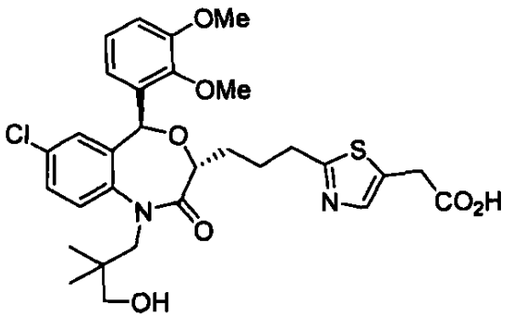
According to a similar manner to that of Example 26, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 3.15 (1H, d, J = 12.0 Hz), 3.40 (1H, d, J = 14.4 Hz), 3.60 (3H, s), 3.65 (1H, d, J = 12.0 Hz), 3.75 (2H, dd, J = 1.5, 6.6 Hz), 3.88 (3H, s), 4.48 (1H, d, J = 14.4 Hz), 4.55 (1H, t, J = 6.6 Hz), 6.18 (1H, s), 6.55 (1H, s), 6.96 (2H, dd, J = 2.7, 7.8 Hz), 7.13 (1H, t, J = 7.8 Hz), 7.32-7.40 (2H, m), 8.71 (1H, s).

Example 121

(2-{3-[(3R,5S)-7-chloro-5-(2,3-diemthoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-

benzoxazepine-3-yl]propyl}-1,3-thiazol-5-yl)acetic acid



(1) Ethyl (diethoxyphosphoryl)acetate (4.76 ml, 24 mmol) was added dropwise to a suspension of sodium hydride (0,88 g, 22 mmol) in THF (108 ml) at 0°C. After stirring for 30 minutes, 3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-3-(2-oxoethyl)-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (10.8 g, 20 mmol) was added. After stirring for 1 hour, the mixture was diluted with ethyl acetate, washed with an aqueous saturated ammonium chloride solution and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain ethyl (2E)-4-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-2-butenoate (11.5 g, 20 mmol, 100%).

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3 H, s) 1.03 (3 H, s) 1.28 (3 H, t, J = 7.06 Hz) 2.03 (3 H, s) 2.74 (2 H, m) 3.53 (1 H, d, J = 14.13 Hz) 3.62 (3 H, s) 3.86 (6 H, m) 4.18 (2 H, q, J =

7.16 Hz) 4.56 (1 H, d, J = 14.13 Hz) 5.90 (1 H, d, J = 15.64 Hz) 6.26 (1 H, s) 6.64 (1 H, m, J = 2.26 Hz) 6.95 (2 H, m) 7.27 (4 H, m).

(2) Ethyl (2E)-4-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-2-butenoate (15 g, 26.1 mmol) obtained in Example 121-(1) was dissolved in methanol (150 ml), magnesium (3.17 g, 131 mmol) was added thereto, and the mixture was stirred for 3 hours. The reaction solution was diluted with ethyl acetate, washed with 1N aqueous hydrochloric acid, an aqueous saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was dissolved in methanol (150 ml), a 1N aqueous sodium hydroxide solution (52 ml) was added, and the mixture was stirred for 2 hours. The reaction solution was concentrated under reduced pressure, and the residue was dissolved in water and washed with ether. The aqueous layer was acidified with 1N aqueous hydrochloric acid and then extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was dissolved in methylene chloride (100 ml), pyridine (6.46 ml, 80 mmol) and acetyl chloride (4.98 ml, 70 mmol) were added thereto, and the mixture was stirred for 1 hour. After

water (50 ml) was added, the reaction solution was stirred for 4 hours and then extracted with ethyl acetate. The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain 4-[(3R,5S)-1-[3-acetoxy-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]butanoic acid (10.9 g, 19.8 mmol, 76%).

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3 H, s) 1.02 (3 H, s) 1.56-2.00 (4 H, m) 2.03 (3 H, s) 2.37 (2 H, t, J = 7.16 Hz) 3.51 (1 H, d, J = 14.13 Hz) 3.61 (3 H, s) 3.70-3.92 (6 H, m) 4.56 (1 H, d, J = 14.13 Hz) 6.24 (1 H, s) 6.63 (1 H, d, J = 2.26 Hz) 6.98 (1 H, s dd, J = 7.54, 2.26 Hz) 7.15-7.37 (4 H, m).

(3) Isobutyl carbonate chloride (0.55 ml, 4.20 mmol) was added to a solution of 4-[(3R,5S)-1-[3-acetoxy-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]butanoic acid (2.0 g, 3.65 mmol) obtained in Example 121-(2) and triethylamine (0.53 ml, 3.83 mmol) in dimethylacetamide (20 ml) at 0°C, and the mixture was stirred at 0°C for 30 minutes. To the reaction solution at 0°C, 4-amino-3-oxobutanoic acid hydrochloride (0.71 g, 4.02 mmol) obtained in Example 1-(2) was added and pyridine (0.47 ml, 5.84 mmol) was then added

dropwise.

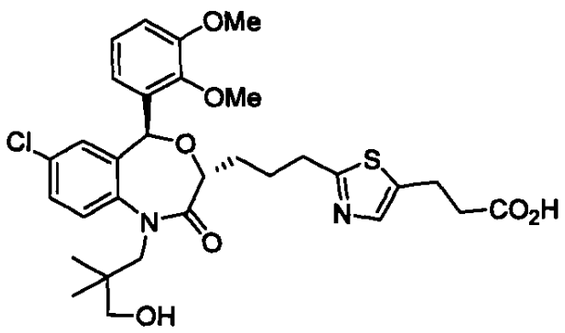
After stirring at room temperature for 1 hour, the reaction solution was diluted with ethyl acetate. This was washed with 1N aqueous hydrochloric acid, a 5% aqueous potassium hydrogen sulfate solution, an aqueous saturated sodium hydrogen carbonate solution and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was dissolved in THF (20 ml), Lawesson's reagent (1.8 g, 4.44 mmol) was added thereto, and the mixture was stirred at 70°C for 1 hour. The reaction solution was diluted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was dissolved in ethanol (20 ml), a 1N aqueous sodium hydroxide solution (10 ml) was added, and the mixture was stirred for 4 hours. The aqueous layer was acidified with a 5% aqueous potassium hydrogen sulfate solution and then extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (1.0 g, 1.66 mmol, 43%).

^{1}H-NMR (DMSO-d_6) δ: 0.76 (3 H, s) 0.83 (3 H, s) 1.63-1.86 (4 H, m) 2.90 (2 H, t, J = 6.78 Hz) 3.02-3.20 (2 H, m)

3.51 (3 H, s) 3.64 (1 H, d, J = 14.13 Hz) 3.78-3.87 (m, 5 H) 4.31 (1 H, d, J = 14.13 Hz) 4.53 (1 H, t, J = 5.09 Hz) 6.05 (1 H, s) 6.38 (1 H, d, J = 2.45 Hz) 7.15 (2 H, d, J = 7.91 Hz) 7.21-7.28 (1 H, m) 7.41 (1 H, s) 7.51 (1 H, dd, J = 8.76, 2.54 Hz,) 7.66 (1 H, d, J = 8.85 Hz).

Example 122

3-(2-{3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]propyl}-1,3-thiazol-5-yl)propionic acid

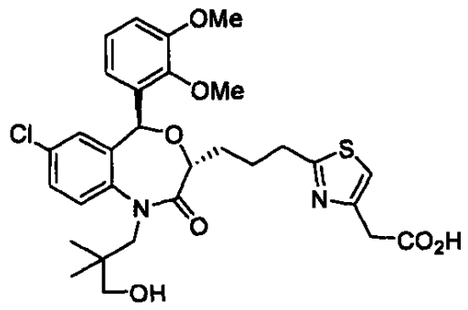


According to a similar manner to that of Example 121, the title compound was obtained.

^{1}H-NMR (DMSO-d_6) δ: 0.75 (3 H, s) 0.83 (3 H, s) 1.59-1.88 (4 H, m) 2.48-2.59 (2 H, m) 2.83-3.20 (6 H, m) 3.51 (3 H, s) 3.64 (1 H, d, J = 14.13 Hz) 3.78-3.86 (4 H, m) 4.31 (1 H, d, J = 14.13 Hz) 4.53 (1 H, t, J = 5.09 Hz) 6.05 (1 H, s) 6.37 (1 H, d, J = 2.45 Hz) 7.11-7.28 (m, 3 H) 7.51 (1 H, dd, J = 8.67, 2.45 Hz) 7.66 (1 H, d, J = 8.85 Hz).

Example 123

(2-{3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-yl]propyl}-1,3-thiazol-4-yl)acetic acid



(1) Diethyl cyanomethylphosphonate (3.88 ml, 24 mmol) was added dropwise to a suspension of sodium hydride (0.88 g, 22 mmol) in THF (108 ml) at 0°C. After stirring for 30 minutes, 3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-3-(2-oxoethyl)-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (10.8 g, 20 mmol) was added. After stirring for 1 hour, the mixture was diluted with ethyl acetate, washed with saturated ammonium chloride and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was dissolved in methanol (105 ml), magnesium (2.4 g, 100 mmol) was added, and the mixture was stirred for 2 hours. The reaction solution was diluted with ethyl acetate, washed with 1N aqueous hydrochloric acid and an aqueous saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and then

concentrated under reduced pressure. The residue was dissolved in methylene chloride (68 ml), triethylamine (3.69 ml, 26.6 mmol) and acetyl chloride (1.51 ml, 21.2 mmol) were added, and the mixture was stirred for 2 hours. The reaction solution was diluted with ethyl acetate, washed with an aqueous saturated sodium hydrogen carbonate solution and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain 3-[(3R,5S)-7-chloro-3-(3-cyanopropyl)-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (5.5 g, 10.4 mmol, 52%).

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3 H, s) 1.02 (3 H, s) 1.66-2.41 (9 H, m) 3.47-3.93 (10 H, m) 4.56 (1 H, d, J = 14.13 Hz) 6.25 (1 H, s) 6.64 (1 H, d, J = 2.26 Hz) 6.99 (1 H, dd, J = 7.25, 2.35 Hz) 7.14-7.39 (4 H, m).

(2) 3-[(3R,5S)-7-chloro-3-(3-cyanopropyl)-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (5.3 g, 10 mmol) obtained in Example 123-(1) was dissolved in a 4N hydrochloric acid-ethyl acetate solution (53 ml). Thereto O,O'-diethyl hydrogen dithiophosphate (2.01 ml, 12 mmol) was added and the mixture was stirred overnight. The reaction solution was washed with water, dried over magnesium sulfate, and

then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain 2-[(3R,5S)-3-(4-amino-4-thioxobutyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-1,1-dimethylethyl acetate (2.8 g, 4.97 mmol, 50%).

MS (ES+) [M+1] 563

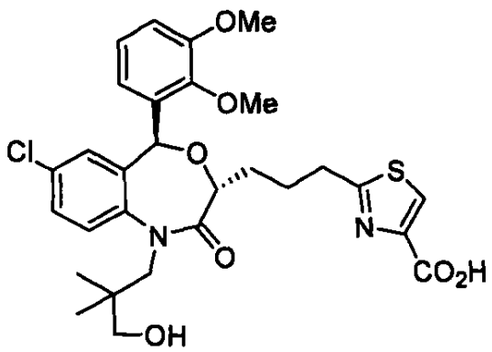
(3) 2-[(3R,5S)-3-(4-amino-4-thioxobutyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-1,1-dimethylethyl acetate (0.563 g, 1.0 mmol) obtained in Example 123-(2) was dissolved in ethanol (10 ml). Thereto ethyl 4-chloro-3-oxobutanoate (0.243 ml, 1.8 mmol) was added and the mixture was stirred at 90°C for 2 hours. After the reaction solution was cooled to room temperature, a 1N aqueous sodium hydroxide solution (5 ml) was added thereto and the mixture was stirred for 5 hours. The aqueous layer was acidified with a 5% aqueous potassium hydrogen sulfate and then extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (0.3 g, 0.498 mmol, 50%).

^{1}H-NMR (DMSO-d_6) δ: 0.76 (3 H, s) 0.83 (3 H, s) 1.63-1.86 (4 H, m) 2.90 (2 H, t, J = 6.78 Hz,) 3.02-3.20 (2 H, m) 3.51 (3 H, s) 3.64 (1 H, d, J = 14.13 Hz) 3.78-3.87 (5 H,

m) 4.31 (1 H, d, J = 14.13 Hz) 4.53 (1 H, t, J = 5.09 Hz) 6.05 (1 H, s) 6.38 (1 H, d, J = 2.45 Hz) 7.15 (2 H, d, J = 7.91 Hz) 7.21-7.28 (1 H, m) 7.41 (1 H, s) 7.51 (1 H, dd, J = 8.76, 2.54 Hz) 7.66 (1 H, d, J = 8.85 Hz).

Example 124

2-{3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]propyl}-1,3-thiazole-4-carboxylic acid

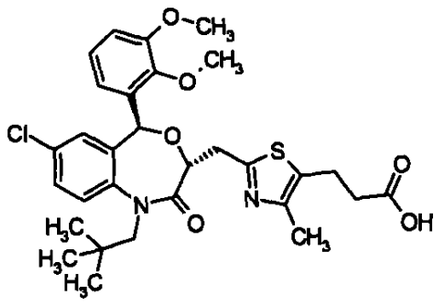


According to a similar manner to that of Example 123, the title compound was obtained.

^{1}H-NMR (DMSO-d_6) δ: 0.75 (3 H, s) 0.83 (3 H, s) 1.67-1.89 (4 H, m) 2.94-3.19 (4 H, m) 3.51 (3 H, s) 3.64 (1 H, d, J = 13.94 Hz) 3.78-3.88 (4 H, m) 4.31 (1 H, d, J = 14.13 Hz) 4.52 (1 H, t, J = 5.27 Hz) 6.05 (1 H, s) 6.37 (1 H, d, J = 2.45 Hz) 7.12-7.28 (3 H, m) 7.50 (1 H, dd, J = 8.76, 2.54 Hz,) 7.66 (1 H, d, J = 8.85 Hz).

Example 125

3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-4-methyl-1,3-thiazol-5-yl)propionic acid

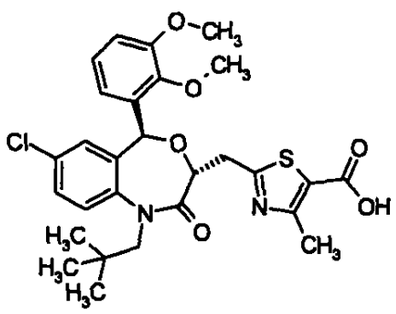


According to a similar manner to that of Example 1, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 2.28 (3H, s), 2.64 (2H, t, J = 7.6 Hz), 3.02 (2H, t, J = 7.6 Hz), 3.31-3.44 (2H, m), 3.52 (1H, dd, J = 15.0, 6.0 Hz), 3.63 (3H, s), 3.89 (3H, s), 4.24-4.30 (1H, m), 4.51 (1H, d, J = 13.8 Hz), 6.31 (1H, s), 6.57 (1H, d, J = 2.1 Hz), 6.97 (1H, dd, J = 6.6, 3.2 Hz), 7.14-7.22 (2H, m), 7.24-7.33 (2H, m).

Example 126

2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-4-methyl-1,3-thiazole-5-carboxylic acid

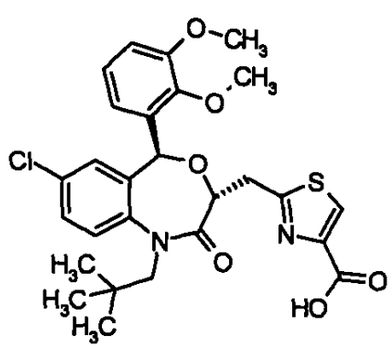


According to a similar manner to that of Example 16, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 2.68 (3H, s), 3.36 (1H, d, J = 13.9 Hz), 3.47 (1H, dd, J = 15.0, 6.9 Hz), 3.55-3.66 (4H, m), 3.89 (3H, s), 4.32 (1H, t, J = 6.4 Hz), 4.52 (1H, d, J = 13.9 Hz), 6.33 (1H, s), 6.59 (1H, d, J = 2.1 Hz), 6.99 (1H, dd, J = 7.5, 2.3 Hz), 7.13-7.23 (2H, m), 7.28-7.35 (2H, m).

Example 127

2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazole-4-carboxylic acid

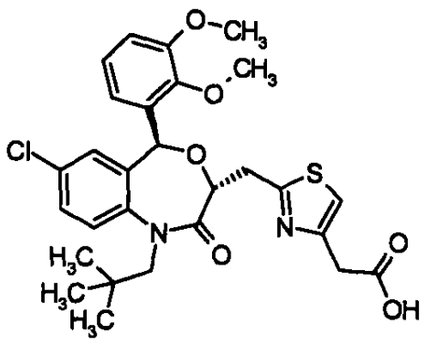


According to a similar manner to that of Example 22, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 3.35 (1H, d, J = 13.9 Hz), 3.50-3.69 (5H, m), 3.89 (3H, s), 4.34 (1H, t, J = 6.4 Hz), 4.50 (1H, d, J = 13.9 Hz), 6.33 (1H, s), 6.58 (1H, d, J = 2.1 Hz), 6.99 (1H, dd, J = 8.0, 1.4 Hz), 7.07-7.12 (1H, m), 7.18 (1H, t, J = 7.9 Hz), 7.25-7.35 (2H, m), 8.19 (1H, s).

Example 128

(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahdyro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-4-yl)acetic acid



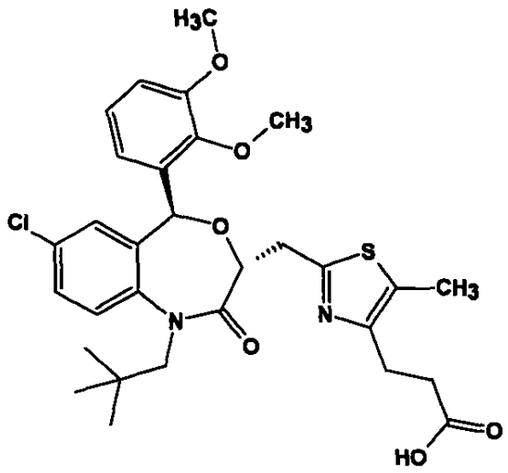
According to a similar manner to that of Example 16, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 3.38 (1H, d, J = 13.9 Hz), 3.48 (1H, dd, J = 15.3, 6.6 Hz), 3.60-3.72 (4H, m), 3.79 (2H, s), 3.89 (3H, s), 4.34 (1H, t, J = 6.5 Hz), 4.49 (1H, d, J = 13.9 Hz), 6.33 (1H, s), 6.60 (1H, s), 6.99 (1H,

dd, J = 6.9, 2.9 Hz), 7.02 (1H, s), 7.13-7.23 (2H, m), 7.33 (2H, s).

Example 129

3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-5-methyl-1,3-thiazol-4-yl)propionic acid

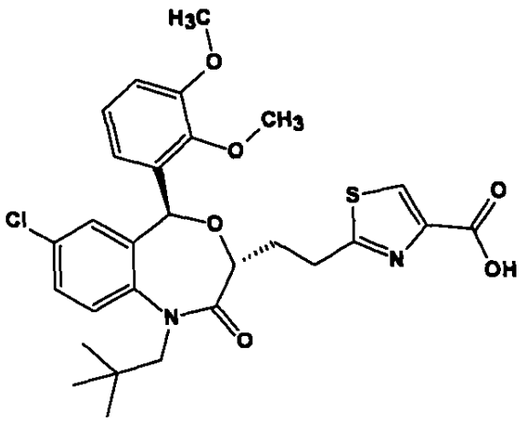


According to a similar manner to that of Example 20, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 2.32 (3H, s), 2.66-2.73 (2H, m), 2.82-2.90 (2H, m), 3.33-3.44 (2H, m), 3.58 (1H, dd, J = 16.2, 6.6 Hz), 3.63 (3H, s), 3.89 (3H, s), 4.27 (1H, t, J = 6.4 Hz), 4.49 (1H, d, J = 13.9 Hz), 6.31 (1H, s), 6.60 (1H, s), 6.99 (1H, dd, J = 5.8, 3.8 Hz), 7.15-7.23 (2H, m), 7.31-7.39 (2H, m, J = 1.9 Hz).

Example 130

2-{2-[(3R,5S)-7-chloro-5-(2.3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3-5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1,3-thiazole-4-carboxylic acid

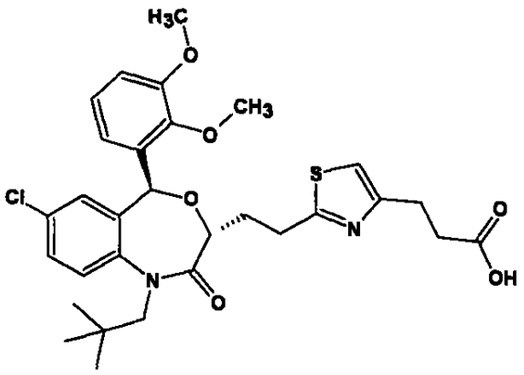


According to a similar manner to that of Example 22, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 2.22-2.49 (2H, m), 3.08-3.32 (2H, m), 3.35 (1H, d, J = 13.9 Hz), 3.63 (3H, s), 3.90 (3H, s), 3.94 (1H, dd, J = 7.5, 5.3 Hz), 4.50 (1H, d, J = 13.8 Hz), 6.28 (1H, s), 6.61 (1H, d, J = 2.3 Hz), 6.95-7.03 (1H, m), 7.16-7.24 (2H, m), 7.25-7.37 (2H, m), 8.11 (1H, s).

Example 131

3-(2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1,3-thiazol-4-yl)propionic acid

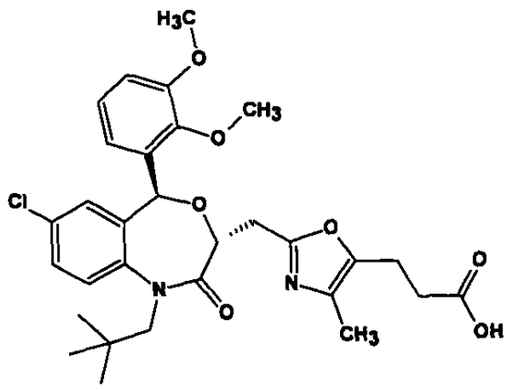


According to a similar manner to that of Example 88, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 2.18-2.44 (2H, m), 2.64-2.74 (2H, m), 2.94-3.03 (2H, m), 3.04-3.27 (2H, m), 3.36 (1H, d, J = 13.9 Hz), 3.63 (3H, s), 3.89 (3H, s), 3.94 (1H, dd, J = 7.3, 5.7 Hz), 4.52 (1H, d, J = 13.9 Hz), 6.28 (1H, s), 6.60 (1H, d, J = 2.1 Hz), 6.80 (1H, s), 6.99 (1H, dd, J = 7.0, 2.6 Hz), 7.16-7.36 (4H, m).

Example 132

3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-4-methyl-1,3-oxazol-5-yl)propionic acid

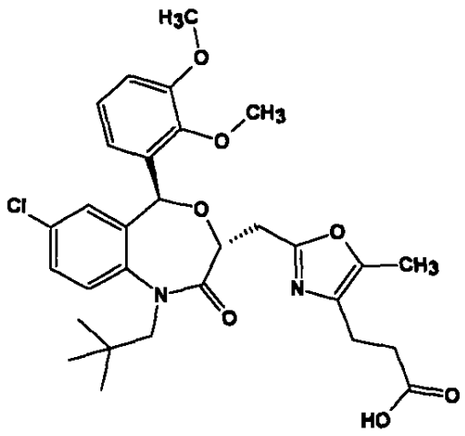


According to a similar manner to that of Example 29, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (9H, s), 2.05 (3H, s), 2.63 (2H, t), 2.88 (2H, t, J = 7.4 Hz), 3.16-3.32 (2H, m), 3.36 (1H, d, J = 13.8 Hz), 3.62 (3H, s), 3.88 (3H, s), 4.38 (1H, t, J = 6.8 Hz), 4.51 (1H, d, J = 13.9 Hz), 6.30 (1H, s), 6.57 (1H, d, J = 1.5 Hz), 6.96 (1H, dd, J = 8.1, 1.3 Hz), 7.03 (1H, dd, J = 7.8, 1.2 Hz), 7.16 (1H, t, J = 7.9 Hz), 7.27-7.36 (2H, m).

Example 133

3-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-5-methyl-1,3-oxazol-4-yl)propionic acid

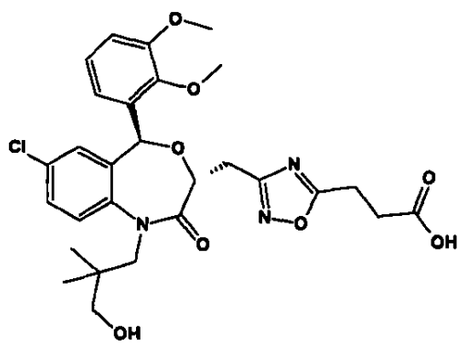


According to a similar manner to that of Example 38, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (9H, s), 2.22 (3H, s), 2.59-2.72 (4H, m), 3.17 (1H, dd, J = 16.0, 6.4 Hz), 3.31-3.45 (2H, m), 3.63 (3H, s), 3.89 (3H, s), 4.40 (1H, t, J = 6.8 Hz), 4.48 (1H, d, J = 13.9 Hz), 6.30 (1H, s), 6.59 (1H, d, J = 2.1 Hz), 6.97 (1H, dd, J = 7.9, 1.5 Hz), 7.08 (1H, dd, J = 7.7, 1.5 Hz), 7.16 (1H, t, J = 7.9 Hz), 7.32-7.42 (2H, m).

Example 134

3-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)propionic acid

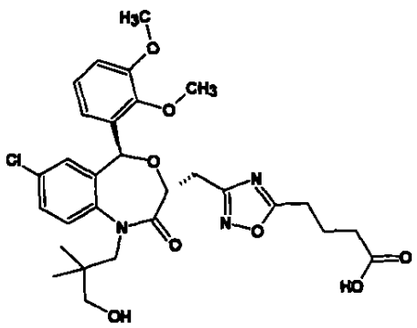


According to a similar manner to that of Example 60, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 2.89 (2H, t, J = 7.2 Hz), 3.11-3.27 (4H, m), 3.34-3.44 (2H, m), 3.58-3.67 (4H, m), 3.89 (3H, s), 4.39-4.51 (2H, m), 6.19 (1H, s), 6.60 (1H, d, J = 1.7 Hz), 6.98 (1H, dd, J = 8.0, 1.6 Hz), 7.07-7.12 (1H, m), 7.18 (1H, t, J = 7.9 Hz), 7.32-7.41 (2H, m).

Example 135

4-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)butanoic acid

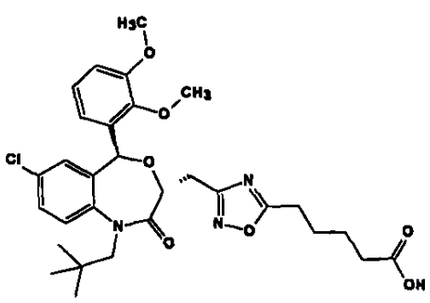


According to a similar manner to that of Example 60, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 2.08-2.19 (3H, m), 2.49 (2H, t, J = 7.2 Hz), 2.95 (2H, t, J = 7.3 Hz), 3.12-3.28 (2H, m), 3.34-3.44 (2H, m), 3.59-3.67 (4H, m), 3.89 (3H, s), 4.41-4.52 (2H, m), 6.20 (1H, s), 6.60 (1H, d, J = 1.5 Hz), 6.98 (1H, dd, J = 8.0, 1.6 Hz), 7.09 (1H, dd, J = 7.8, 1.4 Hz), 7.17 (1H, t, J = 7.9 Hz), 7.35-7.38 (2H, m).

Example 136

5-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic acid



(1) 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (23.0 g, 0.120 mol) and ammonium 1H-1,2,3-benzotriazol-1-olate (18.26 g, 0.120 mol) were added to a solution of [(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetic acid (46.19 g, 0.100 mol) in DMF (500 ml) and the mixture was stirred for 20 hours. The reaction solution was concentrated under reduced pressure, extracted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, and then dried over magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography and then recrystallized from ethyl acetate-hexane to obtain 2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetamide (32.43 g) as a crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9 H, s), 2.65 - 2.73 (1 H, m), 2.84 - 2.92 (1 H, m), 3.37 (1 H, d, J = 13.8 Hz), 3.62 (3 H, s), 3.89 (3 H, s), 4.39 (1 H, dd, J = 7.3, 5.9 Hz), 4.50 (1 H, d, J = 13.9 Hz), 5.27 (1 H, s), 5.86 (1 H, s), 6.28 (1 H, s), 6.61 (1 H, d, J = 2.1 Hz), 6.99 (1 H, dd, J = 6.7, 3.1 Hz), 7.18 - 7.23 (2 H, m), 7.31 - 7.36 (2 H, m).

(2) 1-1'-Carbonylbis-1H-imidazole (9.85 g, 0.0607 mol) and allyl bromide (20.7 ml, 0.243 mol) were added to a

solution of 2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-yl]acetamide (14.0 g, 0.0304 mol) obtained in Example 136-(1) in acetonitrile (140 ml), and the mixture was heated to reflux for 3 hours. After standing to cool, the reaction solution was extracted with ethyl acetate, washed with 1N aqueous hydrochloric acid and an aqueous saturated sodium chloride solution, and then dried over magnesium sulfate. The extract was filtered with silica gel and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to obtain [(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetonitrile (12.31 g).

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9 H, s), 2.78 - 2.88 (1 H, m), 2.89 - 2.99 (1 H, m), 3.38 (1 H, d, J = 13.9 Hz), 3.63 (3 H, s), 3.90 (3 H, s), 4.21 (1 H, dd, J = 7.6, 5.6 Hz), 4.51 (1 H, d, J = 13.9 Hz), 6.30 (1 H, s), 6.65 (1 H, d, J = 2.1 Hz), 7.01 (1 H, d, J = 7.9 Hz), 7.19 - 7.41 (4 H, m).

(3) Triethylamine (23.66 ml, 0.169 mol) was added dropwise to a solution of hydroxylamine hydrochloride (11.77 g, 0.169 mol) in DMSO (150 ml) under ice-cooling and the mixture was stirred for 30 minutes. Precipitates were filtered off. To the filtrate was added [(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-

1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetonitrile (15.0 g, 0.0339 mol) obtained in Example 136-(2) and the mixture was stirred at 80°C for 4 hours. The reaction solution was extracted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain 2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-N'-hydroxyethaneimidoamide (17.5 g) as an amorphous substance, which was used in the next reaction without purification.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9 H, s), 2.56 - 2.64 (1 H, m), 2.79 (1 H, dd, J = 14.4, 7.1 Hz), 3.36 (1 H, d, J = 13.9 Hz), 3.60 - 3.65 (3 H, m), 3.89 (3 H, s), 4.07 - 4.14 (1 H, m), 4.50 (1 H, d, J = 13.9 Hz), 4.98 (2 H, s), 6.25 - 6.29 (1 H, m), 6.60 (1 H, d, J = 2.1 Hz), 6.99 (1 H, dd, J = 5.9, 3.9 Hz), 7.16 - 7.23 (2 H, m), 7.29 - 7.35 (2 H, m).

(4) Triethylamine (0.83 ml, 5.95 mmol) and methyl 6-chloro-6-oxohexanoate (0.69 g, 3.85 mmol) were added dropwise to a solution of 2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-N'-hydroxyethaneimidoamide (1.67 g, 3.5 mmol) obtained in Example 136-(3) in THF (15 ml) under ice-cooling, and the mixture was stirred at room temperature for 2.5 hours. The

reaction solution was concentrated under reduced pressure, water (15 ml) was added thereto, and the mixture was heated to reflux for 11 hours. The reaction solution was extracted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography to obtain methyl 5-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoate (1.04 g).

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9 H, s), 1.63 - 1.91 (4 H, m), 2.36 (2 H, t, J = 7.2 Hz), 2.87 (2 H, t, J = 7.4 Hz), 3.20 - 3.42 (3 H, m), 3.62 (3 H, s), 3.67 (3 H, s), 3.88 (3 H, s), 4.43 (1 H, t, J = 6.8 Hz), 4.51 (1 H, d, J = 13.9 Hz), 6.31 (1 H, s), 6.58 (1 H, s), 6.97 (1 H, dd, J = 8.0, 1.6 Hz), 7.07 (1 H, dd, J = 7.7, 1.5 Hz), 7.15 (1 H, t, J = 7.9 Hz), 7.29 - 7.37 (2 H, m).

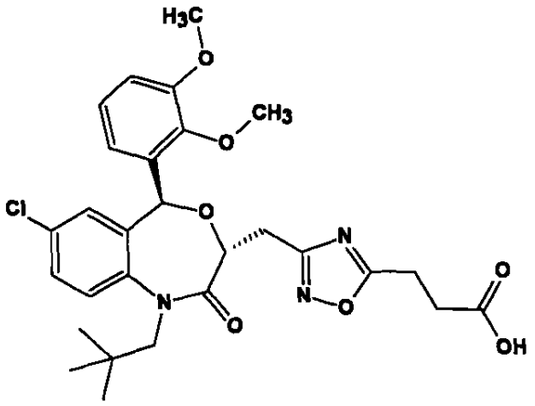
(5) A 2N aqueous sodium hydroxide solution (2.60 ml, 5.20 mmol) was added to a solution of methyl 5-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoate (1.04 g, 1.73 mmol) obtained in Example 136-(4) in ethanol (10 ml) and the mixture was stirred for 13 hours. The reaction

solution was diluted with water and then washed with diethyl ether. The extract solution was acidified with 6N aqueous hydrochloric acid, extracted with ethyl acetate, washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain 3-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic acid (0.89 g).

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 1.66-1.93 (4H, m), 2.39 (2H, t, J = 7.3 Hz), 2.88 (2H, t, J = 7.4 Hz), 3.19-3.41 (3H, m), 3.62 (3H, s), 3.88 (3H, s), 4.43 (1H, t, J = 6.8 Hz), 4.51 (1H, d, J = 13.9 Hz), 6.31 (1H, s), 6.58 (1H, d, J = 1.5 Hz), 6.96 (1H, dd, J = 7.9, 1.7 Hz), 7.07 (1H, dd, J = 7.8, 1.6 Hz), 7.14 (1H, t, J = 7.8 Hz), 7.28-7.37 (2H, m).

Example 137

3-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)propionic acid

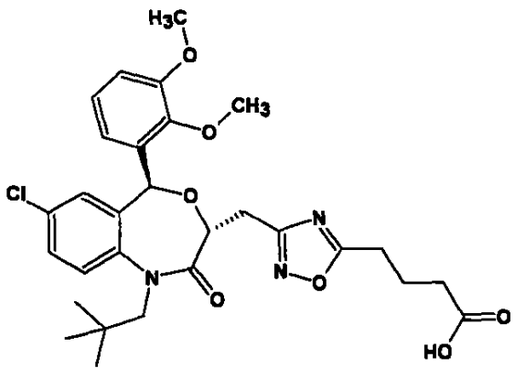


According to a similar manner to that of Example 136, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 2.90 (2H, t, J = 7.3 Hz), 3.16 (2H, t, J = 7.3 Hz), 3.21-3.40 (3H, m), 3.62 (3H, s), 3.88 (3H, s), 4.42 (1H, t, J = 6.7 Hz), 4.51 (1H, d, J = 13.9 Hz), 6.31 (1H, s), 6.59 (1H, d, J = 1.5 Hz), 6.97 (1H, dd, J = 8.0, 1.6 Hz), 7.06-7.11 (1H, m), 7.16 (1H, t, J = 7.9 Hz), 7.29-7.37 (2H, m).

Example 138

4-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)butanoic acid

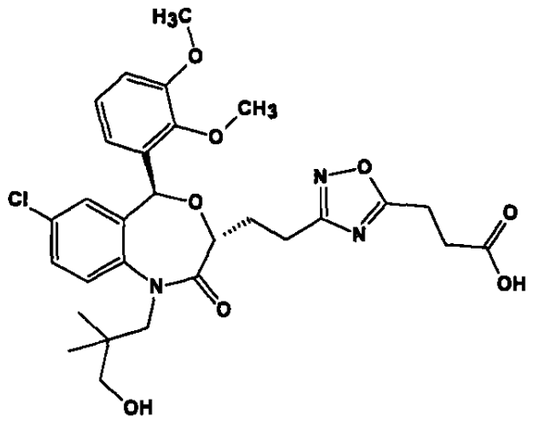


According to a similar manner to that of Example 136, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 2.08-2.20 (2H, m), 2.49 (2H, t, J = 7.1 Hz), 2.95 (2H, t, J = 7.3 Hz), 3.19-3.42 (3H, m), 3.62 (3H, s), 3.88 (3H, s), 4.44 (1H, t, J = 6.8 Hz), 4.51 (1H, d, J = 13.9 Hz), 6.31 (1H, s), 6.59 (1H, s), 6.97 (1H, dd, J = 8.0, 1.8 Hz), 7.08 (1H, dd, J = 7.8, 1.4 Hz), 7.16 (1H, t, J = 7.9 Hz), 7.30-7.36 (2H, m).

Example 139

3-(3-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl)-1,2,4-oxadiazol-5-yl)propionic acid

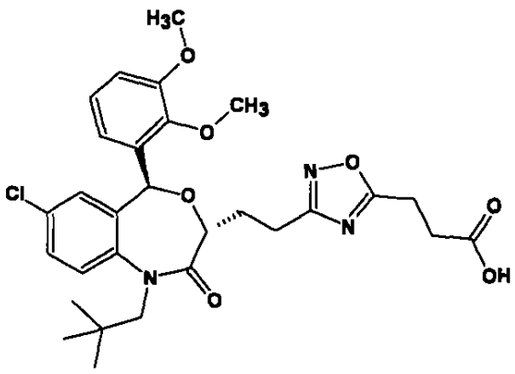


According to a similar manner to that of Example 60, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.15-2.41 (2H, m), 2.77-2.98 (4H, m), 3.07-3.20 (3H, m), 3.37 (1H, d, J = 14.3 Hz), 3.59-3.66 (4H, m), 3.89 (3H, s), 3.95 (1H, dd, J = 7.7, 5.3 Hz), 4.46 (1H, d, J = 14.3 Hz), 6.15 (1H, s), 6.60 (1H, d, J = 2.3 Hz), 6.95-7.02 (1H, m), 7.17-7.22 (2H, m, J = 4.1, 4.1 Hz), 7.29-7.39 (2H, m).

Example 140

3-(3-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1,2,4-oxadiazol-5-yl)propionic acid

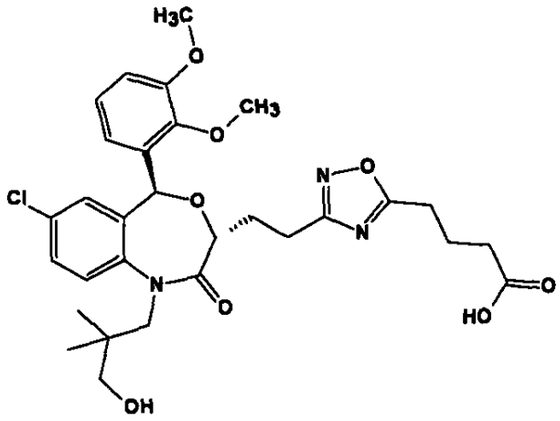


According to a similar manner to that of Example 136, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (9H, s), 2.14-2.41 (2H, m), 2.77-2.98 (4H, m), 3.11 (2H, t, J = 7.3 Hz), 3.34 (1H, d, J = 13.9 Hz), 3.63 (3H, s), 3.89 (3H, s), 3.93 (1H, dd, J = 7.9, 5.1 Hz), 4.51 (1H, d, J = 13.8 Hz), 6.27 (1H, s), 6.60 (1H, d, J = 2.1 Hz), 6.98 (1H, dd, J = 7.0, 2.6 Hz), 7.15-7.24 (2H, m), 7.28-7.36 (2H, m).

Example 141

4-(3-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1,2,4-oxadiazol-5-yl)butanoic acid

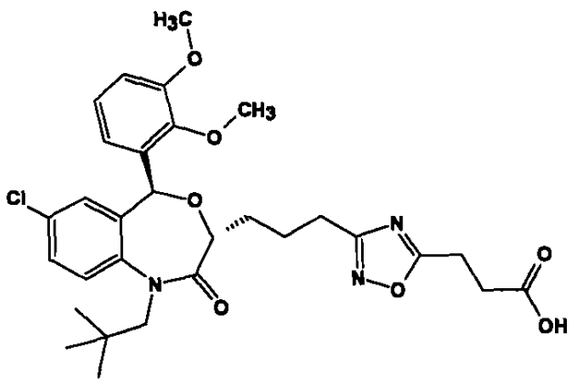


According to a similar manner to that of Example 60, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.02-2.14 (3H, m), 2.18-2.42 (2H, m), 2.45 (2H, t, J = 7.2 Hz), 2.77-2.99 (4H, m), 3.15 (1H, d, J = 12.1 Hz), 3.37 (1H, d, J = 14.3 Hz), 3.58-3.66 (4H, m), 3.89 (3H, s), 3.95 (1H, dd, J = 7.8, 5.4 Hz), 4.46 (1H, d, J = 14.3 Hz), 6.15 (1H, s), 6.60 (1H, d, J = 2.3 Hz), 6.95-7.03 (1H, m), 7.16-7.23 (2H, m), 7.29-7.39 (2H, m).

Example 142

3-(3-{3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]propyl}-1,2,4-oxadiazol-5-yl)propionic acid

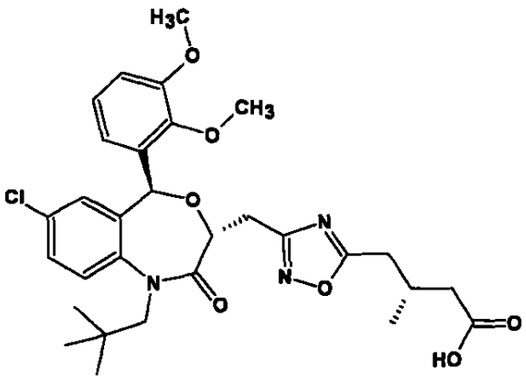


According to a similar manner to that of Example 136, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (9H, s), 1.70-2.03 (4H, m), 2.66-2.78 (2H, m), 2.90 (2H, t, J = 7.2 Hz), 3.15 (2H, t, J = 7.2 Hz), 3.34 (1H, d, J = 13.9 Hz), 3.62 (3H, s), 3.85 (1H, dd, J = 7.5, 4.8 Hz), 3.89 (3H, s), 4.50 (1H, d, J = 13.9 Hz), 6.24 (1H, s), 6.59 (1H, d, J = 2.3 Hz), 6.98 (1H, dd, J = 7.7, 2.1 Hz), 7.15-7.36 (4H, m).

Example 143

(3R)-4-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)-3-methylbutanoic acid

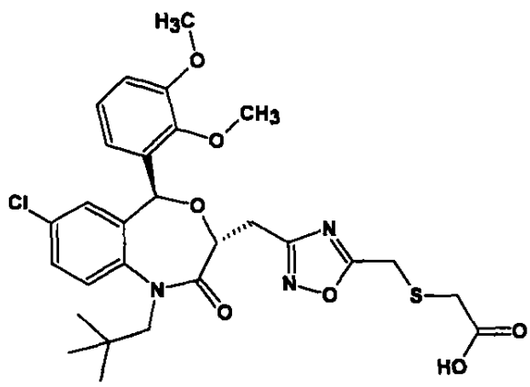


According to a similar manner to that of Example 136, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 1.07 (3H, d, J = 6.6 Hz), 2.33 (1H, dd, J = 15.6, 7.2 Hz), 2.41-2.63 (2H, m), 2.84 (1H, dd, J = 15.3, 6.9 Hz), 2.96 (1H, dd, J = 15.3, 6.6 Hz), 3.21-3.42 (3H, m), 3.62 (3H, s), 3.88 (3H, s), 4.45 (1H, t, J = 6.8 Hz), 4.51 (1H, d, J = 13.9 Hz), 6.31 (1H, s), 6.58 (1H, s), 6.96 (1H, dd, J = 7.9, 1.7 Hz), 7.06 (1H, dd, J = 7.9, 1.5 Hz), 7.14 (1H, t, J = 7.9 Hz), 7.29-7.37 (2H, m).

Example 144

{[(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3-5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)methyl]thio}acetic acid



(1) Potassium thioacetate (0.76 g, 5.97 mmol) was added to a solution of (3R,5S)-7-chloro-3-{[5-(chloromethyl)-1,2,4-oxadiazol-3-yl]methyl}-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-1,5-dihydro-4,1-benzoxazepin-2(3H)-one (3.8 g, 4.98 mmol) synthesized as in Example 136 in DMF (30 ml), and the mixture was stirred at room temperature for 12 hours. The reaction solution was extracted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (4:1)] to obtain S-[(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)methyl] acetate (2.45 g, 4.26 mmol, 86%) as white noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 2.40 (3H, s), 3.30 (2H,

dd, J = 6.7, 2.4 Hz), 3.37 (1H, d, J = 13.9 Hz), 3.62 (3H, s), 3.88 (3H, s), 4.28 (2H, s), 4.42 (1H, t, J = 6.8 Hz), 4.51 (1H, d, J = 13.8 Hz), 6.30 (1H, s), 6.58 (1H, d, J = 1.9 Hz), 6.97 (1H, dd, J = 8.1, 1.5 Hz), 7.05 (1H, dd, J = 7.8, 1.0 Hz), 7.17 (1H, t, J = 8.0 Hz), 7.28-7.37 (2H, m).

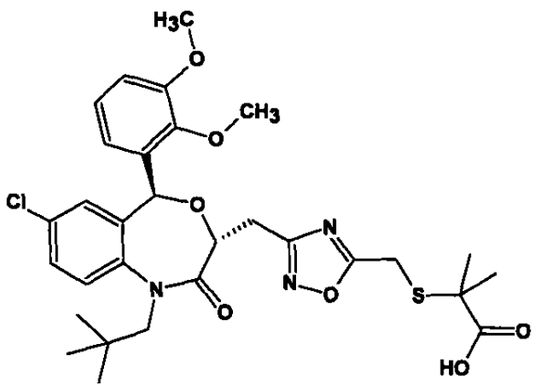
(2) A 2N aqueous sodium hydroxide solution (1.74 ml, 3.48 mmol) was added to a solution of S-[(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)methyl] acetate (1.0 g, 1.74 mmol) in methanol (10 ml), and the mixture was stirred for 1.5 hours. The reaction solution was extracted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. Ethyl bromoacetate (0.12 ml, 1.04 mmol) and potassium carbonate (0.24 g, 1.74 mmol) were added to a solution of the residue in THF (10 ml), and the mixture was stirred of 17 hours. The reaction solution was extracted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was dissolved in ethanol (10 ml), a 2N aqueous sodium hydroxide solution (1.16 ml, 2.33 mmol) was added, and the mixture was stirred for 5 hours. The reaction solution was diluted with water and then

washed with diethyl ether. The extract was acidified with 1N aqueous hydrochloric acid, extracted with ethyl acetate, washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain {[(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)methyl]thio}acetic acid (413 mg, 80%).

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 3.26 (1H, dd, J = 15.7, 6.7 Hz), 3.34-3.44 (4H, m), 3.63 (3H, s), 3.89 (3H, s), 4.00 (2H, s), 4.44-4.54 (2H, m), 6.31 (1H, s), 6.59 (1H, s), 6.97 (1H, dd, J = 8.0, 1.6 Hz), 7.07 (1H, dd, J = 7.9, 1.5 Hz), 7.16 (1H, t, J = 8.0 Hz), 7.34 (2H, d, J = 1.3 Hz).

Example 145

2-{[(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}1,2,4-oxadiazol-5-yl)methyl]thio}-2-methylpropionic acid

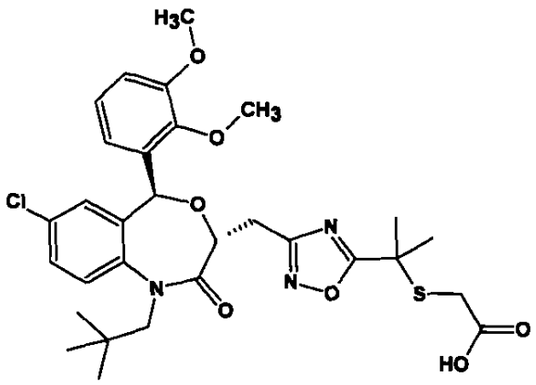


According to a similar manner to that of Example 144, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (9H, s), 1.54 (3H, s), 1.56 (3H, s), 3.20 (1H, dd, J = 15.4, 6.2 Hz), 3.33-3.47 (2H, m), 3.63 (3H, s), 3.89 (3H, s), 4.01 (2H, s), 4.44-4.53 (2H, m), 6.30 (1H, s), 6.60 (1H, s), 6.98 (1H, dd, J = 7.8, 1.8 Hz), 7.12 (1H, dd, J = 7.7, 1.7 Hz), 7.18 (1H, t, J = 7.8 Hz), 7.34 (2H, d, J = 0.9 Hz).

Example 146

{[1-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)-1-methylethyl]thio}acetic acid

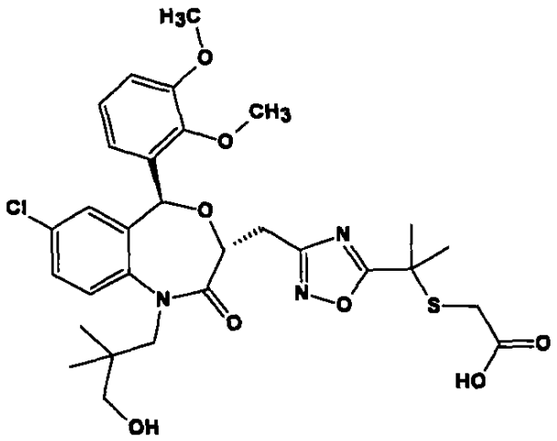


According to a similar manner to that of Example 144, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (9H, s), 1.78 (3H, s), 1.81 (3H, s), 3.15 (1H, dd, J = 15.8, 5.3 Hz), 3.28-3.53 (4H, m), 3.64 (3H, s), 3.89 (3H, s), 4.47 (1H, d, J = 13.9 Hz), 4.53 (1H, dd, J = 8.7, 5.3 Hz), 6.30 (1H, s), 6.62 (1H, s), 6.98 (1H, dd, J = 7.0, 2.8 Hz), 7.13-7.22 (2H, m), 7.36 (2H, d, J = 1.3 Hz).

Example 147

{[1-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)-1-methylethyl]thio}acetic acid

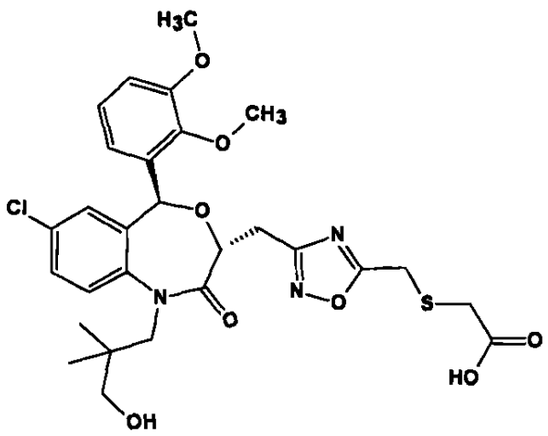


According to a similar manner to that of Example 144, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.67 (3H, s), 1.04 (3H, s), 1.78 (3H, s), 1.79 (3H, s), 3.16-3.27 (2H, m), 3.35-3.49 (4H, m), 3.59-3.67 (4H, m), 3.89 (3H, s), 4.41-4.53 (2H, m), 6.19 (1H, s), 6.61 (1H, s), 6.99 (1H, dd, J = 7.9, 1.9 Hz), 7.11 (1H, dd, J = 7.8, 1.8 Hz), 7.18 (1H, t, J = 7.9 Hz), 7.34-7.43 (2H, m).

Example 148

{[(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)methyl}-1,2,4-oxadiazol-5-yl)methyl]thio}acetic acid

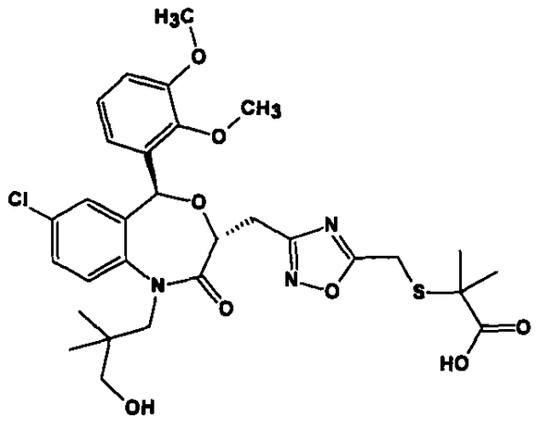


According to a similar manner to that of Example 144, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s), 1.05 (3H, s), 3.17-3.32 (2H, m), 3.34-3.48 (4H, m), 3.58-3.68 (4H, m), 3.89 (3H, s), 4.00 (2H, s), 4.42-4.53 (2H, m), 6.19 (1H, s), 6.61 (1H, d, J = 1.3 Hz), 6.98 (1H, dd, J = 8.1, 1.5 Hz), 7.07 (1H, dd, J = 7.7, 1.5 Hz), 7.17 (1H, t, J = 8.0 Hz), 7.33-7.42 (2H, m).

Example 149

2-{[(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)methyl]thio}-2-methylpropionic acid

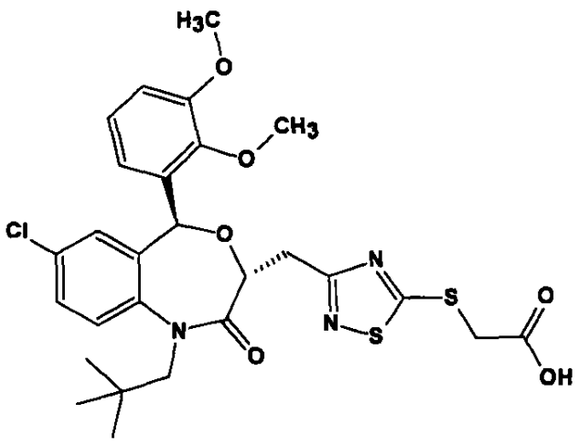


According to a similar manner to that of Example 144, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s), 1.04 (3H, s), 1.54 (3H, s), 1.54 (3H, s), 3.14-3.29 (2H, m), 3.34-3.47 (2H, m), 3.57-3.66 (4H, m), 3.89 (3H, s), 4.03 (2H, s), 4.42-4.52 (2H, m), 6.19 (1H, s), 6.60 (1H, d, J = 1.1 Hz), 6.98 (1H, dd, J = 8.1, 1.7 Hz), 7.09 (1H, dd, J = 7.7, 1.5 Hz), 7.17 (1H, t, J = 7.9 Hz), 7.33-7.41 (2H, m).

Example 150

[(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-thiadiazol-5-yl)thio]acetic acid



(1) Methyl iodide (0.65 ml, 10.48 mmol) was added to a solution of 2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethanethioamide (1.0 g, 2.10 mmol) obtained as in Example 16-(2) in acetone (10 ml), and the mixture was stirred for 14 hours. After the reaction solution was concentrated under reduced pressure, ammonium acetate (0.81 g, 10.48 mmol) and methanol (10 ml) were added thereto and the mixture was heated to reflux for 4 hours. After perchloromethylmercaptan (0.23 ml, 2.1 mmol) was added to a solution of the residue in dichloromethane, a solution of sodium hydroxide (0.375 g, 9.38 mmol) in water (3 ml) was slowly added dropwise thereto at -10°C. The reaction solution was stirred at -10°C for 2 hours and then at room temperature for 30 minutes. The reaction solution was extracted with ethyl acetate, washed successively with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then

concentrated under reduced pressure. The residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (95:5-85:15)] to obtain (3R,5S)-7-chloro-3-[(5-chloro-1,2,4-thiadiazol-3-yl)methyl]-5-(2,3-dimethoxyphenyl)-1-(2,2,dimethylpropyl)-1,5-dihydro-4,1-benzoxazepin-2(3H)-one (0.46 g, 0.857 mmol, 41%) as a white noncrystalline solid.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 3.33-3.48 (2H, m), 3.55-3.66 (4H, m), 3.89 (2H, s), 4.50 (1H, d, J = 13.8 Hz), 4.58 (1H, t, J = 6.7 Hz), 6.31 (1H, s), 6.59 (1H, d, J = 1.1 Hz), 6.93-7.04 (2H, m), 7.15 (1H, t, J = 8.0 Hz), 7.30-7.38 (2H, m).

(2) Ethyl thioglycolate (113 ml, 1.03 mmol) and potassium carbonate (178 mg, 1.29 mmol) were added to a solution of (3R,5S)-7-chloro-3-[(5-chloro-1,2,4-thiadiazol-3-yl)methyl]-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-1,5-dihydro-4,1-benzoxazepin-2(3H)-one (0.46 g, 0.857 mmol) obtained in Example 150-(1) in THF (10 ml), and the mixture was stirred at 45°C for 16 hours. The reaction solution was extracted with ethyl acetate, washed successively with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (95:5-85:15)] to obtain ethyl

[(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-thiadiazol-5-yl)thio]acetate (0.48 g, 0.774 mmol, 90%) as a white noncrystalline solid.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 1.26 (3H, t, J = 7.2 Hz), 3.32-3.43 (2H, m), 3.57 (1H, dd, J = 15.6, 6.9 Hz), 3.63 (3H, s), 3.89 (3H, s), 4.01 (2H, s), 4.18 (2H, q, J = 7.2 Hz), 4.50 (1H, d, J = 13.9 Hz), 4.58 (1H, t, J = 6.7 Hz), 6.31 (1H, s), 6.59 (1H, s), 6.96 (1H, dd, J = 8.1, 1.5 Hz), 7.04 (1H, dd, J = 7.8, 1.4 Hz), 7.15 (1H, t, J = 8.0 Hz), 7.34 (2H, d, J = 1.3 Hz).

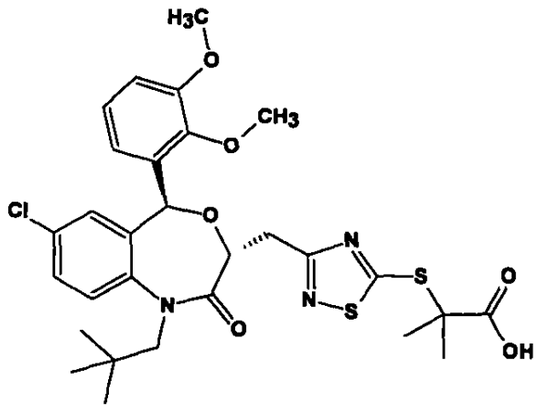
(3) A 2N aqueous sodium hydroxide solution (1.16 ml, 2.32 mmol) was added to a solution of ethyl [(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-thiadiazol-5-yl)thio]acetate (0.48 g, 0.774 mmol) obtained in Example 150-(2) in a mixture of ethanol (5 ml) and THF (5 ml), and the mixture was stirred for 1 hour. The reaction solution was extracted with water and then washed with diethyl ether. The aqueous layer was acidified with 1N aqueous hydrochloric acid, extracted with ethyl acetate, washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was recrystallized from ethanol-hexane to obtain [(3-{[(3R,5S)-7-chloro-5-(2,3-

dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-thiadiazol-5-yl)thio]acetic acid (374 mg, 0.632 mmol, 82%) as a colorless crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 3.34-3.45 (2H, m), 3.57-3.68 (4H, m), 3.89 (3H, s), 3.93 (2H, s), 4.49 (1H, d, J = 13.9 Hz), 4.56 (1H, dd, J = 7.2, 6.2 Hz), 6.31 (1H, s), 6.61 (1H, s), 6.97 (1H, dd, J = 8.1, 1.5 Hz), 7.04 (1H, dd, J = 7.7, 1.3 Hz), 7.16 (1H, t, J = 7.9 Hz), 7.33-7.38 (2H, m).

Example 151

2-[(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-tihadiazol-5-yl)thio]-2-methylpropionic acid



(1) Ethyl 3-mercaptopropionate (0.28 ml, 2.2 mmol) and potassium carbonate (0.21 g, 1.5 mmol) were added to a

solution of (3R,5S)-7-chloro-3-[(5-chloro-1,2,4-thiadiazol-3-yl)methyl]-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-1,5-dihydro-4,1-benzoxazepin-2(3H)-one (0.54 g, 1.0 mmol) obtained in Example 150-(1) in THF (10 ml), and the mixture was stirred at 45°C for 13.5 hours. The reaction solution was extracted with ethyl acetate, washed successively with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was dissolved in ethanol, a 2N aqueous sodium hydroxide solution (0.836 ml, 1.67 mmol) was added, and the mixture was stirred for 1 hour. The reaction solution was extracted with ethyl acetate, washed successively with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. To the residue was added ethyl 2-bromo-2-methylpropionate (0.18 ml, 1.25 mmol), potassium carbonate (0.17 g, 1.25 mmol) and THF (10 ml), and the mixture was heated to reflux for 14 hours. The reaction solution was extracted with ethyl acetate, washed successively with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (85:15-80:20)] to obtain

ethyl 2-[(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-thiadiazol-5-yl)thio]-2-methylpropionate (0.47 g, 87%).

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 1.16 (3H, t, J = 7.1 Hz), 1.66 (3H, s), 1.68 (3H, s), 3.35-3.44 (2H, m), 3.55 (1H, dd, J = 15.6, 6.6 Hz), 3.62 (3H, s), 3.88 (3H, s), 4.06 (2H, ddd, J = 14.2, 7.1, 1.9 Hz), 4.51 (1H, d, J = 13.9 Hz), 4.59 (1H, t, J = 6.8 Hz), 6.30 (1H, s), 6.56 (1H, d, J = 1.9 Hz), 6.93-7.00 (1H, m), 7.13 (1H, t, J = 8.0 Hz), 7.31-7.39 (1H, m).

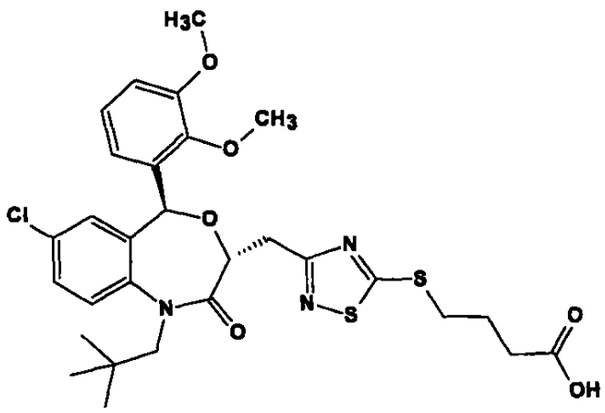
(2) A 2N aqueous sodium hydroxide solution (1.1 ml, 2.17 mmol) was added to a solution of ethyl 2-[(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-thiadiazol-5-yl)thio]-2-methylpropionate (0.47 g, 0.725 mmol) obtained in Example 151-(1) in ethanol (10 ml), and the mixture was stirred for 2 hours. The reaction solution was extracted with water and then washed with diethyl ether. The aqueous layer was acidified with 1N aqueous hydrochloric acid, extracted with ethyl acetate, washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain 2-[(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-

tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-tihadiazol-5-yl)thio]2-methylpropionic acid (332 mg, 74%).

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 1.66 (3H, s), 1.68 (3H, s), 3.34-3.49 (2H, m), 3.56-3.67 (4H, m), 3.89 (3H, s), 4.49 (1H, d, J = 13.9 Hz), 4.57 (1H, t, J = 6.7 Hz), 6.31 (1H, s), 6.58 (1H, d, J = 2.1 Hz), 6.97 (2H, dd, J = 7.1, 5.9 Hz), 7.14 (1H, t, J = 7.9 Hz), 7.31-7.43 (2H, m).

Example 152

4-[(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-thiadiazol-5-yl)thio]butanoic acid



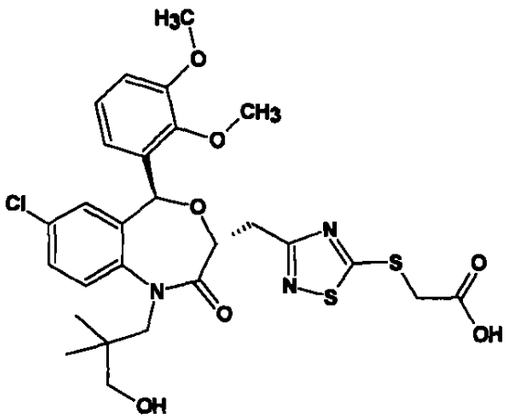
According to a similar manner to that of Example 151, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 2.03-2.15 (2H, m), 2.50 (2H, t, J = 7.1 Hz), 3.29 (2H, dt, J = 7.0, 2.3 Hz), 3.33-3.43 (2H, m), 3.58 (1H, dd, J = 15.6, 6.9 Hz), 3.63 (3H, s), 3.88 (3H, s), 4.50 (1H, d, J = 13.8 Hz), 4.61 (1H,

t, J = 6.7 Hz), 6.31 (1H, s), 6.58 (1H, s), 6.96 (1H, dd, J = 8.1, 1.5 Hz), 7.03 (1H, dd, J = 7.9, 1.1 Hz), 7.14 (1H, t, J = 7.9 Hz), 7.33 (2H, d, J = 1.3 Hz).

Example 153

[(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-thiadiazol-5-yl)thio]acetic acid

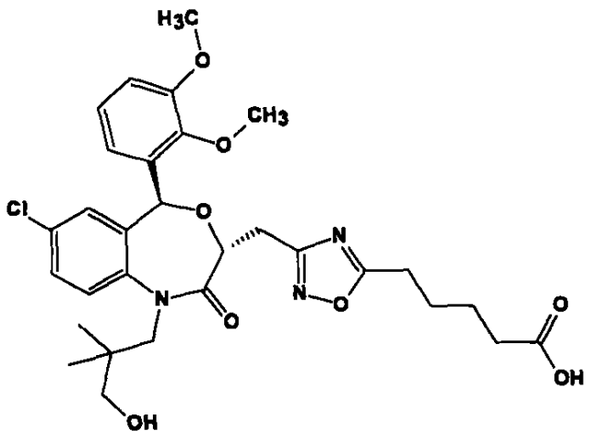


According to a similar manner to that of Example 150, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 3.20 (1H, d, J = 11.9 Hz), 3.35 (1H, dd, J = 15.9, 5.4 Hz), 3.42 (1H, d, J = 14.3 Hz), 3.59-3.71 (5H, m), 3.89 (3H, s), 3.99 (2H, s), 4.46 (1H, d, J = 14.3 Hz), 4.58 (1H, dd, J = 7.9, 5.5 Hz), 6.19 (1H, s), 6.62 (1H, s), 6.98 (1H, dd, J = 8.0, 1.6 Hz), 7.09 (1H, dd, J = 7.9, 1.5 Hz), 7.17 (1H, t, J = 7.9 Hz), 7.35-7.44 (2H, m).

Example 154

5-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic acid



(1) Triethylamine (1.2 ml, 8.5 mmol) and methyl 6-chloro-6-oxohexanoate (0.98 g, 5.5 mmol) were added dropwise to a solution of 3-[(3R,5S)-3-[(2Z)-2-amino-2-(hydroxyimino)ethyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (2.67 g, 5.0 mmol) obtained in Example 58-(1) in THF (25 ml) under ice-cooling, and the mixture was stirred under ice-cooling for 40 minutes and then at room temperature for 1.5 hours. The reaction solution was concentrated under reduced pressure, water (25 ml) was added, and the mixture was heated to reflux for 18 hours. The reaction solution was extracted with ethyl

acetate, washed with water and an aqueous saturated sodium chloride solution, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography to obtain methyl 3-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxodiazol-5-yl)pentanoate (1.73 g).

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3 H, s), 1.03 (3 H, s), 1.65 - 1.90 (4 H, m), 2.03 (3 H, s), 2.35 (2 H, t, J = 7.2 Hz), 2.86 (2 H, t, J = 7.3 Hz), 3.29 (2 H, ddd, J = 30.5, 15.6, 6.7 Hz), 3.55 (1 H, d, J = 13.9 Hz), 3.61 (3 H, s), 3.67 (3 H, s), 3.74 (1 H, d, J = 11.1 Hz), 3.85 (1 H, d, J = 11.1 Hz), 3.88 (3 H, s), 4.42 (1 H, t, J = 6.7 Hz), 4.58 (1 H, d, J = 14.1 Hz), 6.30 (1 H, s), 6.61 (1 H, d, J = 1.5 Hz), 6.97 (1 H, dd, J = 7.9, 1.7 Hz), 7.07 (1 H, dd, J = 7.8, 1.6 Hz), 7.14 (1 H, t, J = 7.9 Hz), 7.29 - 7.38 (2 H, m).

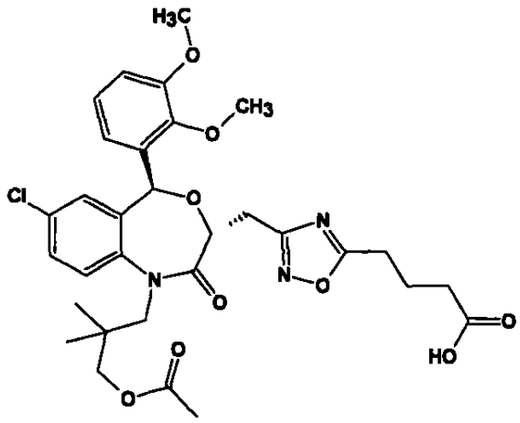
(2) A 2N aqueous sodium hydroxide solution (5.25 ml, 10.5 mmol) was added to a solution of methyl 3-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxodiazol-5-yl)pentanoate (1.73 g, 2.63 mmol) obtained in Example 154-(1) in ethanol (17 ml), and the mixture was stirred for 2 hours. The reaction solution was diluted with water and then washed

with diethyl ether. The extract was acidified with 6N aqueous hydrochloric acid, extracted with ethyl acetate, washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography and then recrystallized from ethyl acetate-hexane to obtain 3-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}1,2,4-oxadiazol-5-yl)pentanoic acid (1.06 g).

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 1.66-1.93 (4H, m), 2.39 (2H, t, J = 7.2 Hz), 2.88 (2H, t, J = 7.4 Hz), 3.12-3.28 (2H, m), 3.33-3.44 (2H, m), 3.57-3.67 (4H, m), 3.89 (3H, s), 4.40-4.53 (2H, m), 6.19 (1H, s), 6.60 (1H, d, J = 1.7 Hz), 6.98 (1H, dd, J = 8.1, 1.7 Hz), 7.09 (1H, dd, J = 7.7, 1.5 Hz), 7.16 (1H, t, J = 7.9 Hz), 7.32-7.41 (2H, m).

Example 155

4-(3-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl}methyl}-1,2,4-oxadiazol-5-yl)butanoic acid

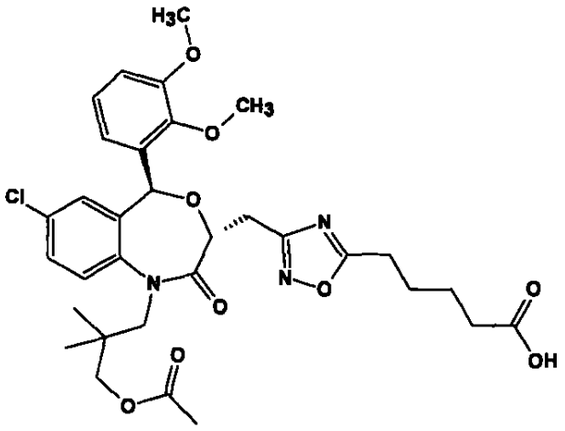


According to a similar manner to that of Example 14, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.03 (3H, s), 2.03 (3H, s), 2.07-2.19 (2H, m), 2.48 (2H, t, J = 7.2 Hz), 2.95 (2H, t, J = 7.3 Hz), 3.24 (1H, dd, J = 15.6, 7.2 Hz), 3.36 (1H, dd, J = 15.6, 6.6 Hz), 3.55 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.74 (1H, d, J = 11.1 Hz), 3.85 (1H, d, J = 11.3 Hz), 3.88 (3H, s), 4.43 (1H, t, J = 6.7 Hz), 4.57 (1H, d, J = 14.1 Hz), 6.30 (1H, s), 6.62 (1H, s), 6.97 (1H, dd, J = 8.0, 1.6 Hz), 7.05-7.10 (1H, m), 7.15 (1H, t, J = 7.8 Hz), 7.30-7.38 (2H, m).

Example 156

5-(3-{[(3R,5S)-1-[3-acetoxy-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxodiazol-5-yl)pentanoic acid

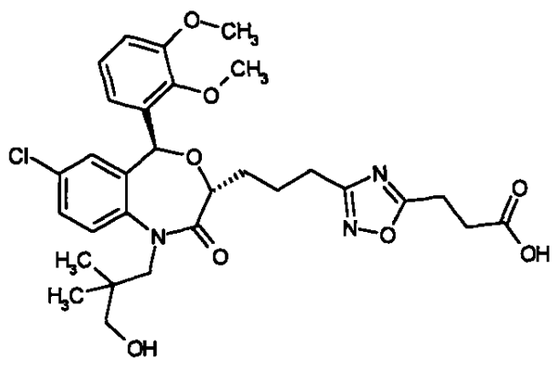


According to a similar manner to that of Example 14, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.03 (3H, s), 1.67 - 1.77 (2H, m), 1.81 - 1.91 (2H, m), 2.03 (3H, s), 2.39 (2H, t, J = 7.2 Hz), 2.88 (2H, t, J = 7.4 Hz), 3.20 - 3.28 (1H, m), 3.30 - 3.38 (1H, m), 3.55 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.72 - 3.77 (1H, m), 3.85 (1H, d, J = 11.1 Hz), 3.88 (3H, s), 4.42 (1H, t, J = 6.7 Hz), 4.57 (1H, d, J = 13.9 Hz), 6.30 (1H, s), 6.61 (1H, d, J = 1.7 Hz), 6.97 (1H, dd, J = 7.9, 1.7 Hz), 7.05 - 7.09 (1H, m), 7.14 (1H, t, J = 7.9 Hz), 7.30 - 7.37 (2H, m).

Example 157

3-(3-{3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]propyl}-1,2,4-oxadiazol-5-yl)propionic acid



(1) (Diethoxyphosphoryl)acetonitrile (5.03 g, 28.4 mmol) was added dropwise to a suspension of sodium hydride (1.14 g, 28.4 mmol) in THF (110 ml) at 0°C. After stirring for 30 minutes, 3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-3-(2-oxoethyl)-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (11.01 g, 21.8 mmol) obtained in Example 115-(1) was added thereto. After stirring for 1 hour, the mixture was diluted with ethyl acetate, washed with an aqueous saturated ammonium chloride solution and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain (2E)-4-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-2-butenenitrile (8.15 g, 71%).

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3 H, s), 1.02 (3 H, s), 2.03 (3 H, s), 2.64 - 3.10 (2 H, m), 3.49 - 3.76 (5 H, m), 3.81 - 4.00 (5 H, m), 4.56 (1 H, dd, J = 14.1, 5.1 Hz), 5.37 -

5.48 (1 H, m), 6.26 (1 H, d, J = 2.6 Hz), 6.62 - 6.80 (2 H, m), 6.96 - 7.04 (1 H, m), 7.12 - 7.39 (4 H, m).

(2) (2E)-4-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-2-butenenitrile (8.15 g, 12.4 mmol) obtained in Example 157-(1) was dissolved in methanol (80 ml), magnesium (1.13 g, 46.4 mmol) was added, and the mixture was stirred for 19 hours. The reaction solution was diluted with ethyl acetate, washed with 1N aqueous hydrochloric acid and an aqueous saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was dissolved in ethyl acetate (40 ml), triethylamine (5.1 ml, 36 mmol) and acetyl chloride (2.0 ml, 29.1 mmol) were added, and the mixture was stirred for 5 hours. The reaction solution was diluted with ethyl acetate, and the organic layer was washed with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain 4-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]butanenitrile (3.89 g, 91%).

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3 H, s), 1.02 (3 H, s), 1.67 - 2.06 (7 H, m), 2.37 (2 H, t, J = 6.7 Hz), 3.52 (1 H, d, J =

14.1 Hz), 3.62 (3 H, s), 3.73 (1 H, d, J = 11.1 Hz), 3.81 - 3.88 (2 H, m), 3.89 (3 H, s), 4.56 (1 H, d, J = 13.9 Hz), 6.25 (1 H, s), 6.64 (1 H, d, J = 2.1 Hz), 7.00 (1 H, dd, J = 7.2, 2.3 Hz), 7.15 - 7.39 (4 H, m).

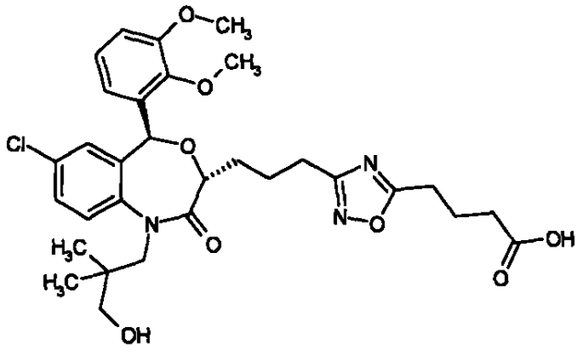
(3) Triethylamine (5.14 ml, 36.7 mmol) was added to a solution of hydroxyamine hydrochloride (2.55 g, 36.7 mmol) in dimethyl sulfoxide (40 ml), and the mixture was stirred for 30 minutes. Insoluble substances were filtered off. To the filtrate was added 4-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]butanenitrile (3.89 g, 7.35 mmol) obtained in Example 157-(2) and the mixture was stirred at 80°C for 6 hours. The reaction solution was diluted with ethyl acetate, and the organic layer was washed with water and an aqueous sodium chloride solution, dried over magnesium sulfate and then concentrated under reduced pressure to obtain 3-[(3R,5S)-3-[4-amino-4-(hydroxyimino)butyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (4.33 g) as crude powder.

(4) According to a similar manner to that of Example 60, the title compound was obtained from 3-[(3R,5S)-3-[4-amino-4-(hydroxyimino)butyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate obtained in Example 157-(3).

^{1}H-NMR ($CDCl_3$) δ: 0.63 (3 H, s), 1.04 (3 H, s), 1.70 - 2.02 (4 H, m), 2.66 - 2.78 (2 H, m), 2.89 (2 H, t, J = 7.2 Hz), 3.10 - 3.20 (3 H, m), 3.36 (1 H, d, J = 14.3 Hz), 3.57 - 3.66 (4 H, m), 3.83 - 3.92 (4 H, m), 4.45 (1 H, d, J = 14.3 Hz), 6.12 (1 H, s), 6.60 (1 H, d, J = 2.3 Hz), 6.99 (1 H, dd, J = 6.4, 3.4 Hz), 7.16 - 7.24 (2 H, m), 7.30 (1 H, d, J = 8.7 Hz), 7.36 (1 H, dd, J = 8.7, 2.4 Hz).

Example 158

4-(3-{3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]propyl}-1,2,4-oxadiazol-5-yl)butanoic acid



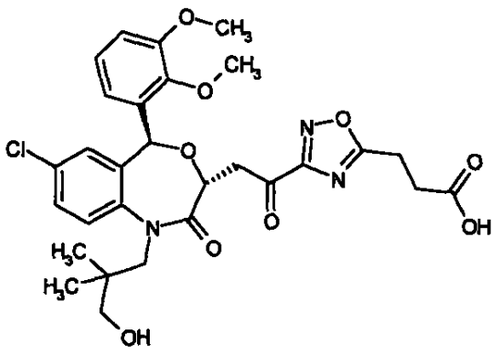
According to a similar manner to that of Example 157, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.63 (3 H, s), 1.04 (3 H, s), 1.71 - 2.02 (4 H, m), 2.08 - 2.20 (2 H, m), 2.49 (2 H, t, J = 7.2 Hz), 2.74 (2 H, t, J = 6.4 Hz), 2.94 (2 H, t, J = 7.3 Hz), 3.15 (1 H, d, J = 12.1 Hz), 3.36 (1 H, d, J = 14.3 Hz),

3.57 - 3.66 (4 H, m), 3.83 - 3.92 (4 H, m), 4.46 (1 H, d, J = 14.3 Hz), 6.13 (1 H, s), 6.60 (1 H, d, J = 2.3 Hz), 6.99 (1 H, dd, J = 6.8, 3.0 Hz), 7.16 - 7.24 (2 H, m), 7.30 (1 H, d, J = 8.7 Hz), 7.36 (1 H, dd, J = 8.7, 2.1 Hz).

Example 159

3-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}-1,2,4-oxadiazol-5-yl)propionic acid



(1) Triethylamine (4.05 ml, 28.9 mmol) was added to a solution of hydroxyamine hydrochloride (2.0 g, 5.78 mmol) in dimethyl sulfoxide (40 ml), and the mixture was stirred for 30 minutes. Insoluble substances were filtered off. To the filtrate was added 3-[(3R,5S)-3-(2-{[tert-butyl(dimethyl)silyl]oxy}-2-cyanoethyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (3.73 g, 5.78 mmol) obtained in Example 115-(2) and the mixture was stirred at 80°C for

2.5 hours. The reaction solution was diluted with ethyl acetate, and the organic layer was washed with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate and then concentrated under reduced pressure to obtain 3-[(3R,5S)-3-[(3Z)-3-amino-2-{[tert-butyl(dimethyl)silyl]oxy}-3-(hydroxyimino)propyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate as crude powder (4.07 g, 100%).

(2) Triethylamine (0.63 ml, 4.49 mmol) and ethyl 4-chloro-4-oxobutanoate (0.47 ml, 3.29 mmol) were added dropwise to a solution of 3-[(3R,5S)-3-[(3Z)-3-amino-2-{[tert-butyl(dimethyl)silyl]oxy}-3-(hydroxyimino)propyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-2,3-dihydro-4,1-benzoxazepin-1(5H)-yl]-2,2-dimethylpropyl acetate (2.03 g, 2.99 mmol) obtained in Example 159-(1) in THF (20 ml) under ice-cooling, and the mixture was stirred at room temperature for 4.5 hours. The reaction solution was concentrated under reduced pressure, water (20 ml) was added to the residue, and the mixture was heated to reflux for 17.5 hours. After the reaction solution was diluted with ethyl acetate, the organic layer was washed with water and an aqueous saturated chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column

chromatography to obtain ethyl 3-[3-(2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-1-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-1,2-4-oxadiazol-5-yl]propionate (1.65 g, 70%).

^{1}H-NMR ($CDCl_3$) δ: -0.07 - 0.11 (6 H, m), 0.69-0.89 (9H, m), 1.04 (3 H, s), 1.09 - 1.15 (3 H, m), 1.29 - 1.38 (3 H, m), 2.09 - 2.14 (3 H, m), 2.32 - 2.60 (2 H, m), 2.85 - 2.95 (2 H, m), 3.18 - 3.29 (2 H, m), 3.61 (1 H, d, J = 14.1 Hz), 3.68 - 3.72 (3 H, m, J = 2.4 Hz), 3.80 - 3.87 (1 H, m), 3.90 - 4.00 (4 H, m), 4.15 - 4.33 (3 H, m), 4.66 (1 H, dd, J = 14.0, 8.2 Hz), 5.12 - 5.29 (1 H, m), 6.34 (1 H, d, J = 12.1 Hz), 6.72 (1 H, dd, J = 10.3, 2.2 Hz), 7.03 - 7.11 (1 H, m), 7.22 - 7.44 (4 H, m).

(3) A boron trifluoride-diethyl ether complex (0.53 ml, 4.19 mmol) was added to a solution of ethyl 3-[3-(2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-1-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-1,2-4-oxadiazol-5-yl]propionate (1.65 g, 2.09 mmol) obtained in Example 159-(2) in acetonitrile (20 ml) under ice-cooling, and the mixture was stirred for 1 hour under ice-cooling. The reaction solution was diluted with ethyl acetate, and the organic layer was washed with water and an aqueous saturated sodium chloride solution, dried over magnesium

sulfate and then concentrated under reduced pressure. To a solution of the residue in dichloromethane (15 ml), triethylamine (0.87 ml, 6.23 ml) was added and a solution of a sulfur trioxide-pyridine complex (0.83 g, 5.19 mmol) in DMSO (3.3 ml) that was prepared previously was then added dropwise. The mixture was stirred for 20 hours. The reaction solution was diluted with ethyl acetate, and the organic layer was washed with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain ethyl 3-(3-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}-1,2,4-oxadiazol-5-yl)propionate (1.05 g, 75%) as crude powder.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (3 H, s), 1.02 (3 H, s), 1.25 (3 H, t, J = 7.2 Hz), 2.02 (3 H, s), 2.90 (2 H, t, J = 7.3 Hz), 3.25 (2 H, t, J = 7.3 Hz), 3.42 (1 H, dd, J = 17.8, 5.4 Hz), 3.57 (1 H, d, J = 14.3 Hz), 3.61 (3 H, s), 3.73 (1 H, d, J = 11.1 Hz), 3.80 - 3.93 (5 H, m), 4.16 (2 H, q, J = 7.2 Hz), 4.54 (1 H, d, J = 14.1 Hz), 4.62 (1 H, dd, J = 8.0, 5.4 Hz), 6.28 (1 H, s), 6.65 (1 H, s), 6.98 (1 H, dd, J = 6.4, 3.2 Hz), 7.13 - 7.21 (2 H, m), 7.36 (2 H, s).

(4) A 2N aqueous sodium hydroxide solution (2.35 ml, 4.68 mmol) was added to a solution of ethyl 3-(3-{[(3R,5S)-

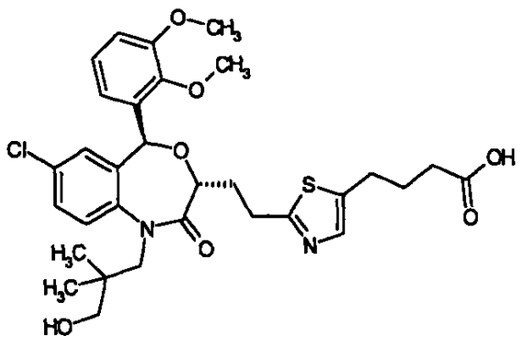
1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}-1,2,4-oxadiazol-5-yl)propionate (1.05 g, 1.562 mmol) obtained in Example 159-(3) in ethanol (10 ml), and the mixture was stirred for 30 minutes. The reaction solution was neutralized with 1N aqueous hydrochloric acid, extracted with ethyl acetate, washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by Gilson preparative HPLC to obtain 3-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}-1,2,4-oxadiazol-5-yl)propionic acid (160 mg, 17%) as powder.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3 H, s), 1.01 - 1.07 (3 H, m), 2.98 (2 H, t, J = 7.1 Hz), 3.16 (1 H, d, J = 12.1 Hz), 3.25 (2 H, t, J = 7.0 Hz), 3.37 - 3.48 (2 H, m), 3.56 - 3.64 (4 H, m), 3.74 (1 H, d, J = 19.6 Hz), 3.82 - 3.96 (5 H, m), 4.43 (1 H, d, J = 14.3 Hz), 4.61 (1 H, dd, J = 8.3, 5.1 Hz), 6.16 (1 H, s), 6.63 (1 H, s), 6.99 (1 H, dd, J = 7.2, 2.6 Hz), 7.13 - 7.23 (2 H, m), 7.40 (2 H, s).

Example 160

4-(2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-

benzoxazepin-3-yl]ethyl}-1,3-thiazol-5-yl)butanoic acid

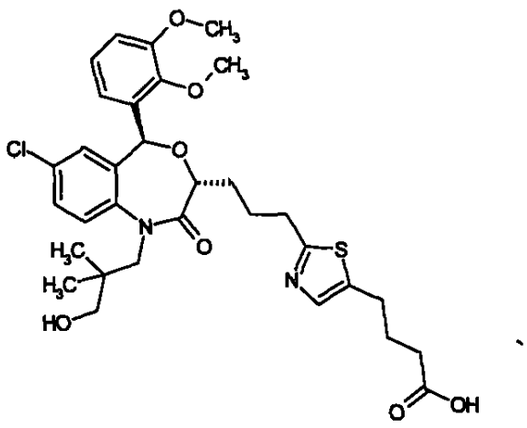


According to a similar manner to that of Example 105, the title compound was obtained

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 1.93 (2H, quintet, J = 7.5 Hz), 2.17-2.42 (4H, m), 3.616 (2H, t, J = 7.5 Hz), 3.622 (1H, d, J = 12.3 Hz), 3.82-3.94 (1H, m), 3.89 (3H, s), 4.45 (1H, d, J = 14.1 Hz), 6.15 (1H, s), 6.61 (1H, d, J = 2.7 Hz), 6.99 (1H, dd, J = 2.4, 7.2 Hz), 7.15-7.25 (2H, m), 7.30 (1H, d, J = 8.7 Hz), 7.35 (1H, dd, J = 2.7, 8.7 Hz).

Example 161

4-(2-{3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]propyl}-1,3-thiazol-5-yl)butanoic acid

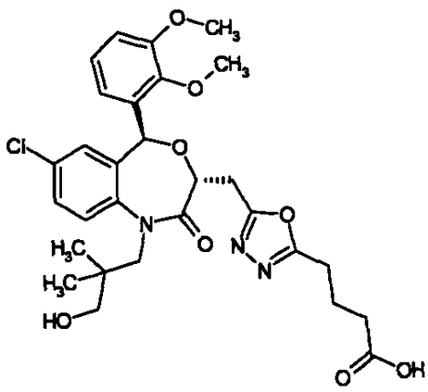


According to a similar manner to that of Example 122, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 1.75-2.05 (6H, m), 2.39 (2H, t, J = 7.5 Hz), 2.84 (2H, J = 7.5 Hz), 2.90-3.01 (2H, m), 3.15 (1H, d, J = 12.0 Hz), 3.35 (1H, d, J = 14.4 Hz), 3.61 (3H, s), 3.62 (1H, d, J = 12.0 Hz), 3.80-3.92 (1H, m), 3.89 (3H, s), 4.46 (1H, d, J = 14.4 Hz), 6.13 (1H, s), 6.60 (1H, d, J = 2.4 Hz), 6.99 (1H, dd, J = 2.7, 7.2 Hz), 7.15-7.25 (2H, m), 7.30 (1H, d, J = 8.4 Hz), 7.31 (1H, s), 7.36 (1H, dd, J = 2.4, 8.4 Hz).

Example 162

4-(5-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3,4-oxadiazol-2-yl)butanoic acid

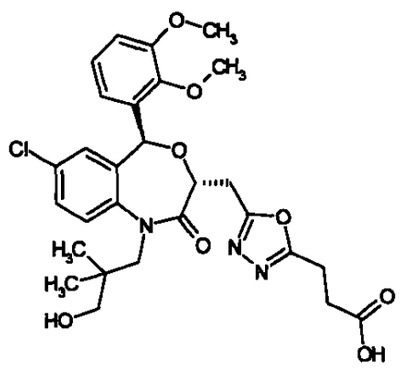


According to a similar manner to that of Example 55, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s), 1.05 (3H, s), 2.12 (2H, quintet, J = 7.2 Hz), 2.49 (2H, t, J = 7.2 Hz), 2.93 (2H, J = 7.2 Hz), 3.17 (1H, d, J = 12.3 Hz), 3.29 (1H, dd, J = 6.6, 15.9 Hz), 3.41 (1H, d, J = 14.4 Hz), 3.47 (1H, dd, J = 6.6, 15.9 Hz), 3.614 (1H, d, J = 12.3 Hz), 3.615 (3H, s), 3.89 (3H, s), 4.46 (1H, d, J = 14.4 Hz), 4.51 (1H, t, J = 6.6 Hz), 6.21 (1H, s), 6.61 (1H, d, J = 2.1 Hz), 6.99 (1H, dd, J = 1.8, 7.8 Hz), 7.08 (1H, dd, J = 1.8, 7.8 Hz), 7.18 (1H, t, J = 7.8 Hz), 7.34-7.43 (2H, m).

Example 163

3-(5-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3,4-oxadiazol-2-ylpropionic acid



(1) Pyridine (0.067 ml, 0.83 mmol) and trifluoromethanesulfonic acid anhydride (0.13 ml, 0.79 mmol) were added to a solution of ethyl (4S)-4-({2-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-yl]acetyl}hydrazino)-4-oxobutanoate (0.25 g, 0.38 mmol) obtained in Example 57-(1) in dichloromethane (4 ml) at -10°C, and the mixture was stirred for 1 hour. After further stirring at 0°C for 1 hour, an aqueous saturated sodium hydrogen carbonate solution (5 ml) was added thereto and the mixture was extracted with dichloromethane (80 ml). The organic layer was washed with water and an aqueous saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [developing solvent: hexane-ethyl acetate (3:2)] to obtain ethyl 3-(5-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3,4-

oxadiazol-2-yl)propionate (0.16 g, 0.25 mmol, 66%) as colorless noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.03 (3H, s), 1.26 (3H, t, J = 7.2 Hz), 2.03 (3H, s), 2.80-2.90 (2H, m), 3.14 (2H, t, J = 7.5 Hz), 3.29 (1H, dd, J = 7.2, 15.9 Hz), 3.43 (1H, dd, J = 6.6, 15.9 Hz), 3.55 (1H, d, J = 14.1 Hz), 3.62 (3H, s), 3.73 (1H, d, J = 10.8 Hz), 3.85 (1H, d, J = 10.8 Hz), 3.89 (3H, s), 4.16 (2H, q, J = 7.2 Hz), 4.42-4.93 (1H, m), 4.55 (1H, d, J = 14.1 Hz), 6.31 (1H, s), 6.63 (1H, d, J = 1.8 Hz), 6.98 (1H, dd, J = 1.5, 8.1 Hz), 7.07 (1H, dd, J = 1.5, 8.1), 7.18 (1H, t, J = 8.1 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.36 (1H, dd, J = 1.8, 8.4 Hz)

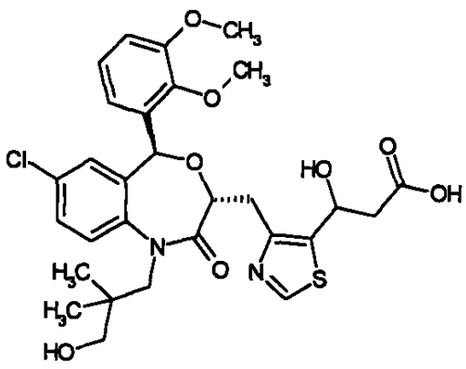
(2) A mixture of ethyl 3-(5-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3,4-oxadiazol-2-yl)propionate (0.1 g, 0.16 mmol) obtained in Example 163-(1), a 1N aqueous sodium hydroxide solution (0.6 ml) and ethanol (5 ml) was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, diluted with water (50 ml), and washed with diethyl ether (10 ml). The aqueous layer was acidified with 1N aqueous hydrochloric acid (1 ml) and then extracted with ethyl acetate (35 ml). The organic layer was washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate and then

concentrated under reduced pressure to obtain 3-(5-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3,4-oxadiazol-2-ylpropionic acid (67 mg, 0.12 mmol, 75%) as a white crystal.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 2.89 (2H, t, J = 7.5 Hz), 3.14 (2H, t, J = 7.5 Hz), 3.17 (1H, d, J = 11.7 Hz), 3.29 (1H, dd, J = 6.3, 15.9 Hz), 3.61 (3H, s), 3.62 (1H, d, J = 11.7 Hz), 3.89 (3H, s), 4.46 (1H, d, J = 14.4 Hz), 4.44-4.52 (1H, m), 6.20 (1H, s), 6.61 (1H, d, J = 1.8 Hz), 6.99 (1H, dd, J = 1.5, 8.1 Hz), 7.07 (1H, dd, J = 1.5, 8.1 Hz), 7.18 (1H, t, J = 8.1 Hz), 7.32-7.42 (2H, m).

Example 164

3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)-3-hydroxypropionic acid



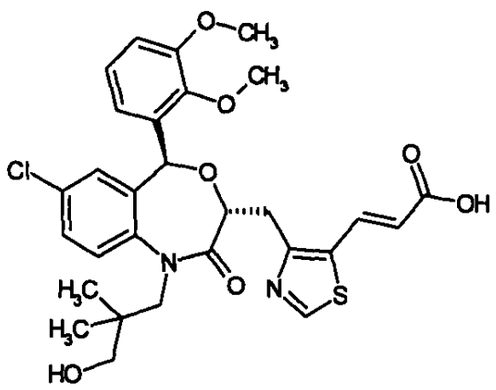
According to a similar manner to that of Example 18,

the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.01 (3/2H, s), 1.04 (3/2H, s), 2.67-2.87 (2H, m), 3.10-3.22 (2H, m), 3.28-3.40 (2H, m), 3.49 (1H, dd, J = 7.8, 14.1 Hz), 3.62 (3H, s), 3.59-3.68 (1H, m), 3.88 (3/2H, s), 3.89 (3/2H, s), 4.37-4.54 (2H, m), 5.56 (1/2H, t, J = 5.7 Hz), 5.65 (1/2H, dd, J = 4.5, 8.7 Hz), 6.18 (1H, s), 6.52 (1/2H, d, J = 2.1 Hz), 6.57 (1/2H, d, J = 2.1 Hz), 6.86-7.04 (2H, m), 7.10-7.20 (1H, m), 7.25-7.36 (2H, m), 8.58 (1/2H, s), 8.61 (1/2H, s).

Example 165

(2E)-3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acrylic acid



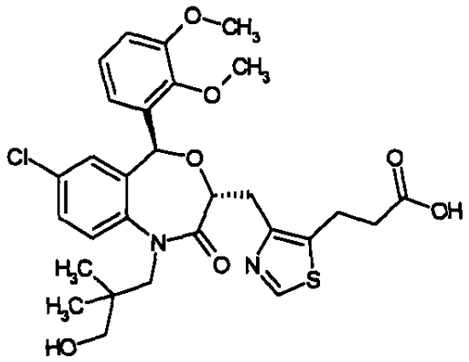
According to a similar manner to that of Example 19, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 3.19 (1H, d, J = 12.0 Hz), 3.32-3.51 (3H, m), 3.61 (3H, s), 3.67 (1H,

d, J = 12.0 Hz), 3.87 (3H, s), 4.39 (1H, t, J = 6.0 Hz), 4.47 (1H, d, J = 14.4 Hz), 6.169 (1H, d, J = 15.6 Hz), 6.173 (1H, s), 6.54 (1H, d, J = 1.8 Hz), 6.85-6.97 (2H, m), 7.09 (1H, t, J = 8.1 Hz), 7.26-7.37 (2H, m), 8.03 (1H, d, J = 15.6 Hz), 8.67 (1H, s)

Example 166

3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)propionic acid

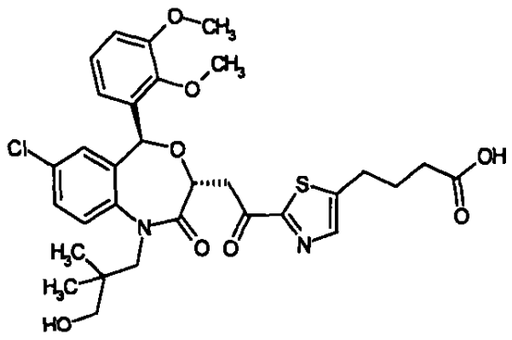


According to a similar manner to that of Example 88, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 2.66 (2H, t, J = 7.5 Hz), 3.10-3.40 (6H, m), 3.61 (3H, s), 3.66 (1H, d, J = 12.0 Hz), 3.88 (3H, s), 4.38-4.46 (2H, m), 6.17 (1H, s), 6.53 (1H, d, J = 2.4 Hz), 6.90-7.00 (2H, m), 7.13 (1H, t, J = 7.8 Hz), 7.26-7.38 (2H, m), 8.52 (1H, s).

Example 167

4-(2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}-1,3-thiazol-5-yl)butanoic acid

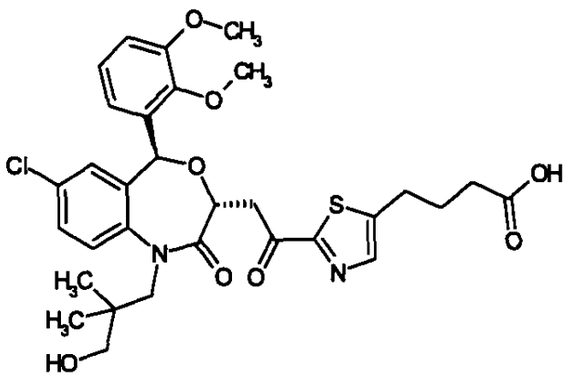


According to a similar manner to that of Example 115, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 1.95-2.10 (2H, m), 2.43 (1H, t, J = 7.2 Hz), 2.97 (2H, t, J = 7.2 Hz), 3.14 (1H, d, J = 12.0 Hz), 3.41 (1H, d, J = 14.1 Hz), 3.55 (1H, dd, J = 4.8, 18.3 Hz), 3.61 (3H, s), 3.63 (1H, d, J = 12.0 Hz), 3.89 (3H, s), 3.95 (1H, dd, J = 8.4, 18.3 Hz), 4.48 (1H, d, J = 14.1 Hz), 4.58 (1H, dd, J = 4.8, 8.4 Hz), 6.17 (1H, s), 6.62 (1H, s), 6.95-7.00 (1H, m), 7.13-7.21 (2H, m), 7.36-7.42 (2H, m), 7.70 (1H, s).

Example 168

3-(5-{[(3R,5S)-7-chloro-5-(2,3-dimethylphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}-2-thienyl)propionic acid



According to a similar manner to that of Example 119, the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 1.04 (3H, s), 2.75 (2H, t, J = 7.2 Hz), 3.09-3.21 (3H, m), 3.27 (1H, dd, J = 4.5, 16.5 Hz), 3.40 (1H, d, J = 14.4 Hz), 3.58-3.74 (2H, m), 3.61 (3H, s), 3.89 (3H, s), 4.47 (1H, d, J = 14.4 Hz), 4.58 (1H, dd, J = 4.5, 8.4 Hz), 6.18 (1H, s), 6.62 (1H, s), 6.89 (1H, d, J = 3.6 Hz), 6.98 (1H, dd, J = 3.0, 7.2 Hz), 7.10-7.21 (2H, m), 7.35-7.42 (2H, m), 7.63 (1H, d, J = 3.6 Hz).

The agent for preventing or treating hyperlipemia of the present invention can be produced, for example, by the following formulations.

In the following formulations, ingredients (additives) other than the active ingredient may be products listed in Japanese Pharmacopoeia, Japanese Pharmaceutical Codex or Japanese Pharmaceutical Excipients.

Preparation Example 1

Capsule

(1) (2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetic acid 10 mg

(2) Lactose 90 mg

(3) Microcrystalline cellulose 70 mg

(4) Magnesium stearate 10 mg

One capsule 180 mg

(1), (2) and (3) and 1/2 of (4) are mixed and then granulated. Thereto is added the remainder of (4) and the whole is encapsulated into a gelatin capsule.

Preparation Example 2

Capsule

(1) (2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetic acid 10 mg

(2) Lactose 90 mg

(3) Microcrystalline cellulose 70 mg

(3) Magnesium stearate 10 mg

One capsule 180 mg

(1), (2) and (3) and 1/2 of (4) are mixed and then granulated. Thereto is added the remainder of (4) and the

whole is encapsulated into a gelatin capsule.

Preparation Example 3

Capsule

(1) (2E)-3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)propionic acid 10 mg

(2) Lactose 90 mg

(3) Microcrystalline cellulose 70 mg

(4) Magnesium stearate 10 mg

One capsule 180 mg

(1), (2) and (3) and 1/2 of (4) are mixed and then granulated. Thereto is added the remainder of (4) and the whole is encapsulated into a gelatin capsule.

Preparation Example 4

Capsule

(1) (5-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic acid 10 mg

(2) Lactose 90 mg

(3) Microcrystalline cellulose 70 mg

(4) Magnesium stearate 10 mg

One capsule 180 mg

(1), (2) and (3) and 1/2 of (4) are mixed and then granulated. Thereto is added the remainder of (4) and the whole is encapsulated into a gelatin capsule.

Preparation Example 5

Tablet

(1) (2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetic acid 10 mg

(2) Lactose 35 mg

(3) Corn starch 150 mg

(4) Microcrystalline cellulose 30 mg

(5) Magnesium stearate 5 mg

One tablet 230 mg

(1), (2), (3), 2/3 of (4) and 1/2 of (5) are mixed and then granulated. To the granule added are the remainders of (4) and (5) and the mixture is compressed into a tablet.

Preparation Example 6

Tablet

(1) (2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetic acid 10 mg

(2) Lactose	35 mg
(3) Corn starch	150 mg
(4) Microcrystalline cellulose	30 mg
(5) Magnesium stearate	5 mg
One tablet	230 mg

(1), (2), (3), 2/3 of (4) and 1/2 of (5) are mixed and then granulated. To the granule added are the remainders of (4) and (5) and the mixture is compressed into a tablet.

Preparation Example 7

Tablet

(1) (2E)-3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)propionic acid 10 mg

(2) Lactose	35 mg
(3) Corn starch	150 mg
(4) Microcrystalline cellulose	30 mg
(5) Magnesium stearate	5 mg
One tablet	230 mg

(1), (2), (3), 2/3 of (4) and 1/2 of (5) are mixed and then granulated. To the granule added are the remainders of (4) and (5) and the mixture is compressed into a tablet.

Preparation Example 8

Tablet

(1) (5-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic acid 10 mg

(2) Lactose 35 mg

(3) Corn starch 150 mg

(4) Microcrystalline cellulose 30 mg

(5) Magnesium stearate 5 mg

One tablet 230 mg

(1), (2), (3), 2/3 of (4) and 1/2 of (5) are mixed and then granulated. To the granule added are the remainders of (4) and (5) and the mixture is compressed into a tablet.

Preparation Example 9

Injection

(1) (2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetic acid 10 mg

(2) Inositol 100 mg

(3) Benzyl alcohol 20 mg

One ampule 130 mg

(1), (2) and (3) are dissolved in distilled water for injection so that the total volume is 2 ml and then filled

into an ampule. All steps are performed under sterile condition.

Preparation Example 10

Injection

(1) (2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-thiazol-5-yl)acetic acid 10 mg

(2) Inositol 100 mg

(3) Benzyl alcohol 20 mg

One ampule 130 mg

(1), (2) and (3) are dissolved in distilled water for injection so that the total volume is 2 ml and then filled into an ampule. All steps are performed under sterile condition.

Preparation Example 11

Injection

(1) (2E)-3-(4-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}phenyl)propionic acid 10 mg

(2) Inositol 100 mg

(3) Benzyl alcohol 20 mg

One ampule 130 mg

(1), (2) and (3) are dissolved in distilled water for injection so that the total volume is 2 ml and then filled into an ampule. All steps are performed under sterile condition.

Preparation Example 12

Injection

(1) (5-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic acid	10 mg
(2) Inositol	100 mg
(3) Benzyl alcohol	20 mg
One ampule	130 mg

(1), (2) and (3) are dissolved in distilled water for injection so that the total volume is 2 ml and then filled into an ampule. All steps are performed under sterile condition.

Experimental Example 1

Squalene synthase inhibitory activity

Measuring method

Squalene synthase inhibitory activity was measured using an enzyme solution obtained according to the following preparation method.

That is, an enzyme solution (protein 0.8 μg) prepared according to the following preparation method was added to a solution (total amount 50 μl) containing 5 μM [1-3H] farnesyl pyrophosphate (specific activity 25 μCi/mole), 1mM NADPH (reduced-type nicotinamide adenine dinucleotide phosphate), 5mM $MgCl_2$, 6mM glutathione, 100mM potassium phosphate buffer (pH7.4) and a test drug (added as an aqueous solution or a DMSO solution) and reacted at 37°C for 45 minutes. After stopping the reaction by addition of 150 μl of chloroform/methanol (1:2) mixed solution, 50 μl of chloroform and 50 μl of a 3N sodium hydroxide solution were added. Then, 50 μl of the chloroform layer (lower layer) containing the reaction product whose main component was squalene was mixed with 3 ml of a toluene-based liquid scintillator and its radioactivity was measured with a liquid scintillation counter.

Squalene synthase inhibitory activity was expressed as the concentration of a test drug required to inhibit 50% of radioactivity incorporated into the chloroform layer (IC_{50}, molar concentration (M)). All compounds described in Examples exhibited potent squalene synthesis inhibitory activity having IC_{50} of 1 μM or lower.

Preparation of a human enzyme solution

Human liver cancer cell HepG2 (about 1×10^9cells)

obtained by culturing in Dulbecco's modified Eagle medium containing 10% bovine fetal serum (37°C in the presence of 5%CO_2) was suspended in 10 ml of an ice-cooled buffer [100mM potassium phosphate buffer (pH7.4), 30mM nicotinamide, 2.5mM $MgCl_2$], disrupted by sonication (30 seconds, twice) and then centrifuged at 10000 x g for 20 minutes (4°C). The resulting supernatant was further centrifuged at 105000 x g for 90 minutes (4°C). The precipitate was suspended in an ice-cooled 100mM potassium phosphate buffer (pH7.4) and then centrifuged at 105000 x g for 90 minutes (4°C). The precipitate was suspended in an ice-cooled 100mM potassium phosphate buffer (pH7.4) (protein concentration about 4 mg/ml). This suspension was used as an enzyme solution.

As seen from the above results, the compound of the present invention has superior squalene synthase inhibitory activity.

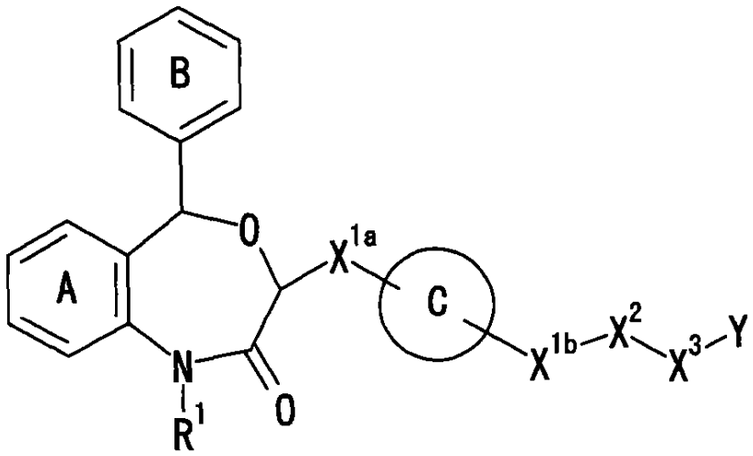
Industrial Applicability

Since the compound of the present invention has squalene synthase inhibitory activity, cholesterol lowering activity and triglyceride lowering activity and has high selectivity for transition to a target organ and a wide safety margin, it is useful as an agent for preventing or treating hyperlipemia as a lipid lowering agent and is also

useful for preventing or treating arteriosclerosis.

CLAIMS

1. A compound represented by the formula [1]:



wherein ring A and ring B each represent an optionally substituted benzene ring, ring C represents an optionally further substituted aromatic ring, R^1 represents a lower alkyl group optionally substituted with an optionally substituted hydroxyl group, X^{1a} represents a bond or optionally substituted lower alkylene, X^{1b} represents a bond or optionally substituted lower alkylene, X^2 represents a bond, -O- or -S-, X^3 represents a bond or an optionally substituted divalent hydrocarbon group, and Y represents an optionally esterified or amidated carboxyl group, or a salt thereof.

2. The compound according to claim 1, wherein X^{1b} is a bond and Y is an optionally esterified carboxyl group.

3. The compound according to claim 1, wherein ring A is a

benzene ring substituted with halogen atom(s).

4. The compound according to claim 1, wherein ring B is a benzene ring substituted with lower alkoxy group(s).

5. The compound according to claim 1, wherein ring C is an optionally further substituted monocyclic aromatic heterocyclic ring.

6. The compound according to claim 1, wherein ring C is an optionally further substituted benzene ring.

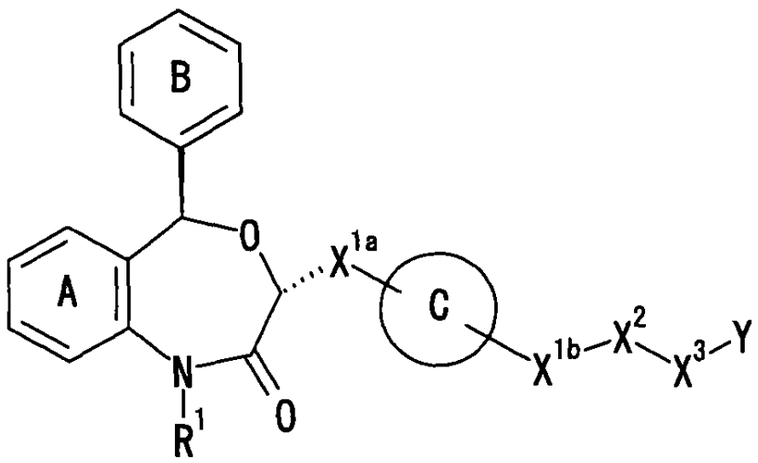
7. The compound according to claim 1, wherein ring C is an optionally further substituted aromatic ring having no hydrogen atom that may be deprotonated.

8. The compound according to claim 1, wherein X^{1a} is C_{1-3} alkylene.

9. The compound according to claim 1, wherein X^2 is a bond.

10. The compound according to claim 1, wherein X^3 is C_{1-4} alkylene.

11. The compound according to claim 1, wherein the formula [I] is the formula [Ia]:



wherein respective symbols are as defined in claim 1.

12. 3-(2-{3-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]propyl}-1,3-thiazol-5-yl)propionic acid, 3-(2-{2-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]ethyl}-1,3-thiazol-4-yl)propionic acid, or a salt thereof.

13. (2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)propionic acid, (2-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,3-oxazol-5-yl)acetic acid, or a salt thereof.

14. 5-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic

acid, 5-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic acid, 5-(3-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic acid, or a salt thereof.

15. A prodrug of the compound according to claim 1.

16. A medicine comprising the compound according to claim 1 or a prodrug thereof.

17. A medicine comprising a combination of the compound according to claim 1 or a prodrug thereof and a cholesterol lowering agent.

18. The medicine according to claim 16 or 17, which is a squalene synthase inhibitor.

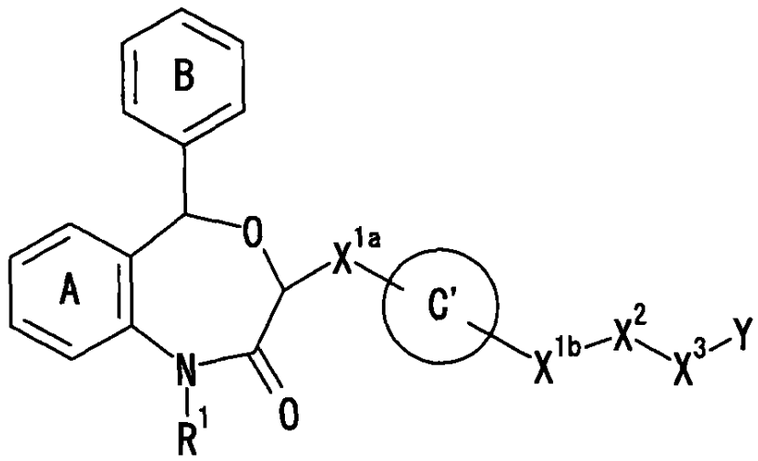
19. The medicine according to claim 16 or 17, which is a triglyceride lowering agent.

20. The medicine according to claim 16 or 17, which is a lipid lowering agent.

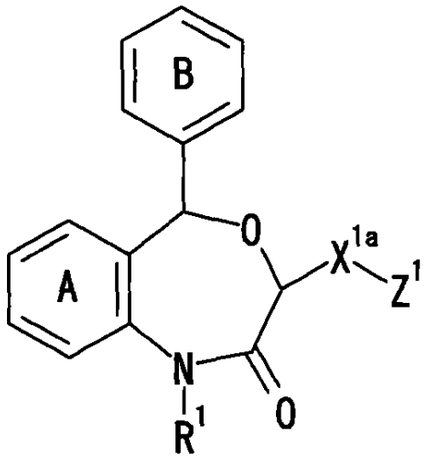
21. The medicine according to claim 16 or 17, which is an agent for preventing or treating hyperlipemia.

22. The medicine according to claim 16 or 17, which is a high density lipoprotein-cholesterol level elevating agent.

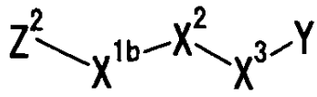
23. A process for preparing a compound represented by the formula [I']:



wherein ring C' represents an optionally further substituted aromatic heterocyclic ring and other symbols are as defined in claim 1, or a salt thereof, which comprises reacting a compound represented by the formula:



wherein Z^1 represents a functional group involved in an aromatic heterocyclic ring forming reaction and other symbols are as defined in claim 1, or a salt thereof, with a compound represented by the formula:



wherein Z^2 represents a functional group involved in an aromatic heterocyclic ring forming reaction and other symbols are as defined in claim 1, or a salt thereof.

24. A method of inhibiting squalene synthase in a mammal, which comprises administering an effective amount of the compound according to claim 1 or a prodrug thereof to said mammal.

25. A method of lowering triglyceride level in a mammal, which comprises administering an effective amount of the compound according to claim 1 or a prodrug thereof to said mammal.

26. A method of lowering lipid level in a mammal, which comprises administering an effective amount of the compound according to claim 1 or a prodrug thereof to said mammal.

27. A method of preventing or treating hyperlipemia in a mammal, which comprises administering an effective amount of the compound according to claim 1 or a prodrug thereof to said mammal.

28. A method of elevating high density lipoprotein-cholesterol level in a mammal, which comprises administering an effective amount of the compound according to claim 1 or a prodrug thereof to said mammal.

29. Use of the compound according to claim 1 or a prodrug

for manufacture of a squalene synthase inhibitor.

30. Use of the compound according to claim 1 or a prodrug thereof for manufacture of a triglyceride lowering agent.

31. Use of the compound according to claim 1 or a prodrug thereof for manufacture of a lipid lowering agent.

32. Use of the compound according to claim 1 or a prodrug thereof for manufacture of an agent for preventing or treating hyperlipemia.

33. Use of the compound according to claim 1 or a prodrug thereof for manufacture of a high density lipoprotein-cholesterol level elevating agent.

COMPUESTO DE BENZOXAZEPINA

CAMPO DE LA INVENCION

La presente invención se refiere a un compuesto de benzoxazepina novedoso que tiene actividad inhibidora de escualeno sintasa, actividad reductora de colesterol y actividad reductora de triglicéridos, que es útil para prevenir o tratar hiperlipemia y similares.

ANTECEDENTES DE LA INVENCION

El incremento anormal de la concentración de lípidos del suero sanguíneo se denomina hiperlipidemia o hiperlipemia. Los lípidos del suero sanguíneo incluyen colesterol (éster de colesterol, colesterol libre), fosfolípido (lecitina, esfingomielina y similares), triglicéridos (lípido neutro), ácido graso libre, otros esteroles y similares, y específicamente, el incremento de colesterol y triglicérido es un asunto clínico (COMMON DISEASE SERIES No.19 hyperlipemia, Haruo Nakamura ed., publicado el 10 de octubre de 1991, por Nankodo).

Ejemplos de un fármaco para reducir el nivel de colesterol en la sangre incluyen fármacos que atrapan ácido biliar e inhiben su absorción tal como colestiramina y

colestipol (por ejemplo, descrito en U.S.P. 4,027,009) y fármacos que inhiben acil coenzima A colesterol aciltransferasa (ACAT) y suprimen la absorción intestinal de colesterol, tal como melinamida. Además, fármacos que inhiben la biosíntesis de colesterol, tales como Lovastatina (descrito en U.S.P. 4,231,938), Simvastatina (descrito en U.S.P. 4,444,784) y Pravastatina (descrito en U.S.P. 4,346,227) que inhiben 3-hidroxi-3-metilglutaril coenzima A (HMG-CoA) reductasa, se usan como medicamentos.

Además, como agentes reductores de triglicérido, derivados de ácido fíbrico tales como clofibrato (patente británica No. 860303), fenofibrato (patente alemana No.2250327) y similares se usan como medicamentos.

Por otra parte, como compuestos que tienen efecto inhibidor sobre la biosíntesis de colesterol al inhibir escualeno sintasa se describen en publicaciones que no son patentes tales como Journal of Medicinal Chemistry, 1988, vol.31, p.1869-1871; Expert Opinion on Therapeutic Patents, 1998, vol.8, p.521-530; Bioorganic Medicinal Chemistry, 2002, vol.10, p.385-400; Bioorganic Medicinal Chemistry, 2002, vol.10, p.401-412; Chemical & Pharmaceutical Bulletin, 2002, vol.50, p.53-58; Chemical & Pharmaceutical Bulletin, 2002, vol.50, p.59-65; Journal of Medicinal Chemistry, 2002, vol.45, p.4571-4580; y publicaciones de patente tales como JP-A 1-213288, JP-A 2-101088, JP-A 2-235820, JP-A 2-235821,

JP-A 3-20226, JP-A 3-68591, JP-A 3-148288, JP-A 9-087260, USP 5135935, USP 5726306, USP 5698691, EP 0645377, WO 92/15579, WO 93/09115, WO 95/021834, WO 97/10224, WO 2001/98282 y USP 6537987.

BREVE DESCRIPCION DE LA INVENCION

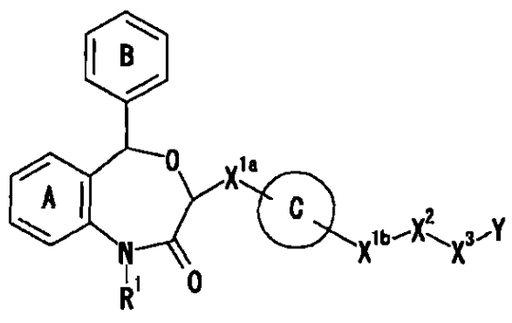
Es muy importante controlar la concentración de lípidos del suero sanguíneo apropiadamente para prevenir o tratar varias enfermedades asociadas con arterioesclerosis que incluyen enfermedades cardiacas isquémicas e infarto cerebral. Además, se piensa que la hipertrigliceridemia induce trastorno pancreático. Cuando la HMG-CoA reductasa es inhibida con un inhibidor de HMG-CoA reductasa, no sólo la biosíntesis de colesterol, sino también la biosíntesis de otros componentes esencialmente un organismo vivo tal como ubiquinona, dolicol y heme A son inhibidos, lo que da por resultado efectos secundarios de interés. Además, el uso de combinación de un agente reductor de triglicérido y un compuesto de estatina es contraindicado debido a toxicidad hepática. Por otra parte, la escualeno sintasa es una enzima que participa en una etapa esencial de la vía de la biosíntesis de colesterol. Esta enzima cataliza la dimerización reductiva de dos moléculas de farnesil pirofosfato para formar escaleno.

Bajo tales circunstancias, un objeto de la presente invención es proveer un compuesto que sea más seguro y que tenga actividad reductora de lípidos más potente tal como actividad inhibidora de escualeno sintasa (actividad reductora de colesterol) y actividad reductora de triglicéridos, y por lo tanto es útil como un fármaco para prevenir o tratar hiperlipemia.

Los inventores de la presente estudiaron intensivamente y, como resultado, por primera vez, sintetizaron un compuesto de 4,1-benzoxazepina caracterizado por una estructura química que tiene un sustituyente particular en la posición 3 y encontraron que este compuesto tiene efectos farmacéuticos inesperadamente excelentes tales como efecto reductor de lípidos con base en su estructura química única, tiene suministro elevado en transferencia a un órgano objetivo y tiene un amplio margen de seguridad, que dio por resultado que se completara la presente invención.

Es decir, la presente invención se refiere a:

(1) un compuesto representado por la fórmula [1]:



en donde el anillo A y el anillo B representan cada uno un anillo de benceno opcionalmente sustituido, el anillo C representa un anillo aromático opcionalmente sustituido adicional, R^1 representa un grupo alquilo inferior opcionalmente sustituido con un grupo hidroxilo opcionalmente sustituido, X^{1a} representa un enlace o alquileno inferior opcionalmente sustituido, X^{1b} representa un enlace o alquileno inferior opcionalmente sustituido, X^2 representa un enlace, -O- o -S-, X^3 representa un enlace o un grupo hidrocarburo divalente opcionalmente sustituido, e Y representa un grupo carboxilo opcionalmente esterificado o amidado, o una sal del mismo;

(2) el compuesto de conformidad con (1) anterior, en donde X^{1b} es un enlace e Y es un grupo carboxilo opcionalmente esterificado;

(3) el compuesto de conformidad con (1) anterior, en donde el anillo A es un anillo de benceno sustituido con átomo(s) de halógeno;

(4) el compuesto de conformidad con (1) anterior, en donde el anillo B es un anillo de benceno sustituido con grupo(s) alcoxi inferior;

(5) el compuesto de conformidad con (1) anterior, en donde el anillo C es un anillo heterocíclico aromático monocíclico opcionalmente sustituido adicional;

(6) el compuesto de conformidad con (1) anterior,

en donde el anillo C es un anillo de benceno opcionalmente sustituido adicional;

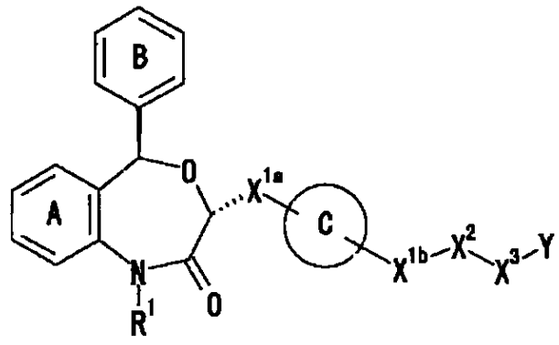
(7) el compuesto de conformidad con (1) anterior, en donde el anillo C es un anillo aromático opcionalmente sustituido adicional que no tiene átomo de hidrógeno que puede ser desprotonado;

(8) el compuesto de conformidad con (1) anterior, en donde X^{1a} es alquileno de C_{1-3};

(9) el compuesto de conformidad con (1) anterior, en donde X^2 es un enlace;

(10) el compuesto de conformidad con (1) anterior, en donde X^3 es alquileno de C_{1-4};

(11) el compuesto de conformidad con (1) anterior, en donde la fórmula [I] es la fórmula [Ia]:



en donde los símbolos respectivos son como se define en (1) anterior;

(12) Acido 3-(2-{3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]propil}-1,3-tiazol-5-

il)propiónico, ácido 3-(2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,3-tiazol-4-il)propiónico, o una sal de los mismos;

(13) Acido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)propiónico, ácido 2-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-isobutil-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)acético, o una sal de los mismos;

(14) Acido 5-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)pentanoico, ácido 5-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)pentanoico, ácido 5-(3-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)pentanoico, o una sal de los mismos;

(15) un profármaco del compuesto de conformidad con (1) anterior;

(16) una medicina que comprende el compuesto de conformidad con (1) anterior o un profármaco del mismo;

(17) una medicina que comprende una combinación del compuesto de conformidad con (1) anterior o un profármaco del mismo y un agente reductor de colesterol;

(18) la medicina de conformidad con (6) o (17) anteriores, que es un inhibidor de escualeno sintasa;

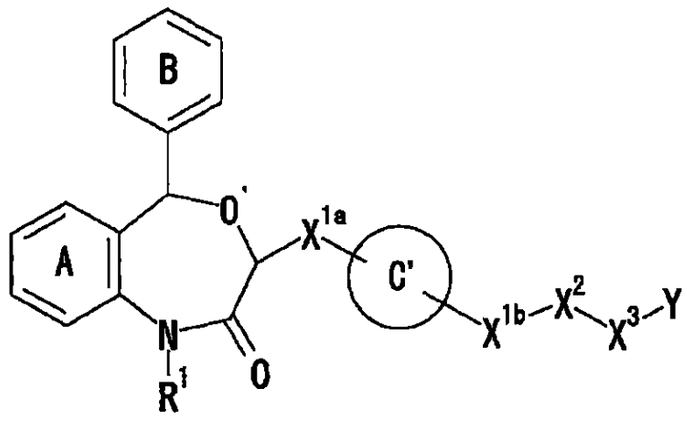
(19) la medicina de conformidad con (6) o (17) anteriores, que es un agente reductor de triglicéridos;

(20) la medicina de conformidad con (6) o (17) anteriores, que es un agente reductor de lípidos;

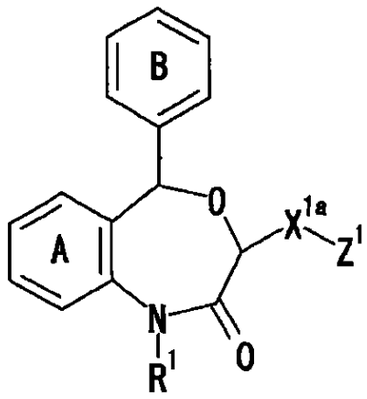
(21) la medicina de conformidad con (6) o (17) anteriores, que es un agente para prevenir o tratar hiperlipemia;

(22) la medicina de conformidad con (6) o (17) anteriores, que es un agente elevador del nivel de colesterol-lipoproteína de alta densidad;

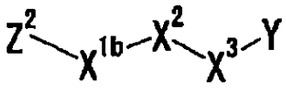
(23) un procedimiento para preparar un compuesto representado por la fórmula [I']:



en donde el anillo C' representa un anillo heterocíclico aromático opcionalmente sustituido adicional y otros símbolos son como se define en (1) anterior, o una sal del mismo, que comprende hacer reaccionar un compuesto representado por la fórmula:



en donde Z^1 representa un grupo funcional implicado en una reacción formadora de anillo heterocíclico aromático y otros símbolos son como se define en (1) anterior, o una sal del mismo, con un compuesto representado por la fórmula:



en donde Z^2 representa un grupo funcional implicado en una reacción formadora de anillo heterocíclico aromático y otros símbolos que se definen en (1) anterior, o una sal del mismo;

(24) un método para inhibir escualeno sintasa en un mamífero, que comprende administrar una cantidad efectiva del

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compuesto de conformidad con (1) anterior o un profármaco del mismo al mamífero;

(25) un método para reducir el nivel de triglicéridos en un mamífero que comprende administrar una cantidad efectiva del compuesto de conformidad con (1) anterior o un profármaco del mismo al mamífero;

(26) un método para reducir el nivel de lípidos en un mamífero, que comprende administrar una cantidad efectiva del compuesto de conformidad con (1) anterior o un profármaco del mismo al mamífero;

(27) un método para prevenir o tratar hiperlipemia en un mamífero, que comprende administrar una cantidad efectiva del compuesto de conformidad con (1) anterior o un profármaco del mismo al mamífero;

(28) un método para elevar el nivel de colesterol-lipoproteína de alta densidad en un mamífero, que comprende administrar una cantidad efectiva del compuesto de conformidad con (1) anterior o un profármaco del mismo al mamífero;

(29) el uso del compuesto de conformidad con (1) anterior o un profármaco para la fabricación de un inhibidor de escualeno sintasa;

(30) el uso del compuesto de conformidad con (1) anterior o un profármaco del mismo para la fabricación de un agente reductor de triglicéridos;

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(31) el uso del compuesto de conformidad con (1) anterior o un profármaco del mismo para la fabricación de un agente reductor de lípidos;

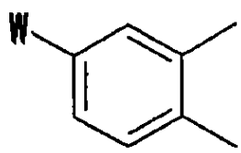
(32) el uso del compuesto de conformidad con (1) anterior o un profármaco del mismo para la fabricación de un agente para prevenir o tratar hiperlipemia;

(33) el uso del compuesto de conformidad con (1) anterior o un profármaco del mismo para la fabricación de un agente elevador del nivel de colesterol-lipoproteína de alta densidad; y similares.

DESCRIPCIÓN DETALLADA DE LA INVENCION

El sustituyente del "anillo de benceno opcionalmente sustituido" representado por el anillo A incluye halógeno (v.gr., flúor, cloro, bromo, yodo), un grupo alquilo inferior opcionalmente sustituido que tiene 1 a 4 átomos de carbono (v.gr., metilo, etilo, propilo, butilo, ter-butilo etc.), un grupo alcoxi inferior opcionalmente sustituido que tiene 1 a 4 átomos de carbono (v.gr., metoxi, etoxi, propoxi, isopropoxi, butoxi, ter-butoxi etc.), un grupo hidroxilo, un grupo nitro y ciano. El anillo A puede tener 1 a 3, preferiblemente 1 a 2 de estos sustituyentes. Los sustituyentes adyacentes de estos sustituyentes se pueden tomar juntos para formar un anillo. El sustituyente del grupo

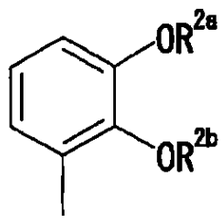
alquilo inferior opcionalmente sustituido que tiene 1 a 4 átomos de carbono o el grupo alcoxi inferior opcionalmente sustituido que tiene 1 a 4 átomos de carbono incluye halógeno (v.gr., flúor, cloro, bromo, yodo), y 1 a 3 sustituyentes pueden estar en posiciones sustituibles opcionales. El anillo A es preferiblemente un anillo de benceno sustituido con átomos de halógeno, etc., muy preferiblemente un anillo de benceno sustituido con un átomo de cloro. El anillo A es preferiblemente un anillo de benceno representado por la fórmula:



en donde W representa un átomo de halógeno (v.gr., flúor, cloro, bromo, yodo) y entre otros, W es preferiblemente un átomo de cloro.

El sustituyente del "anillo de benceno opcionalmente sustituido" representado por el anillo B incluye el mismo número de los mismos grupos que aquellos anteriormente ilustrados como el sustituyente del "anillo de benceno opcionalmente sustituido" representado por el anillo A. el anillo B es preferiblemente un anillo de benceno sustituido con un grupo alcoxi inferior que tiene 1 a 4 átomos de carbono, y entre otros, preferiblemente un anillo

de benceno representado por la fórmula:



en donde R^{2a} y R^{2b} representan independientemente un átomo de hidrógeno o un grupo alquilo inferior que tiene 1 a 4 átomos de carbono (v.gr., metilo, etilo, propilo, butilo etc.) y en particular preferiblemente R^{2a} y R^{2b} son ambos grupos metilo.

El anillo aromático del "anillo de hidrocarburo aromático opcionalmente sustituido adicional" representado por el anillo C incluye un anillo de hidrocarburo aromático y un anillo de hidrocarburo heterocíclico aromático. El anillo de hidrocarburo aromático incluye, por ejemplo, un anillo de benceno, un anillo de naftaleno y similares, y se prefiere un anillo de benceno. El anillo heterocíclico aromático (el anillo heterocíclico aromático del " anillo heterocíclico aromático opcionalmente sustituido adicional" representado por el anillo C') incluye, por ejemplo, un anillo heterocíclico aromático que contiene por lo menos uno (preferiblemente 1 a 4, muy preferiblemente 1 a 2) de 1 a 3 tipos (preferiblemente 1 ó 2 tipos) de heteroátomos seleccionados de un átomo de oxígeno, un átomo de azufre, un átomo de nitrógeno y similares, como átomos que constituyen

el sistema de anillo (átomos de anillo).

El anillo heterocíclico aromático incluye anillos heterocíclicos aromáticos monocíclicos de 5 a 6 miembros tales como furano, tiofeno, pirrol, oxazol, isoxazol, tiazol, isotiazol, imidazol, pirazol, 1,2,3-oxadiazol, 1,2,4-oxadiazol, 1,3,4-oxadiazol, furazano, 1,2,3-tiadiazol, 1,2,4-tiadiazol, 1,3,4-tiadiazol, 1,2,3-triazol, 1,2,4-triazol, tetrazol, piridina, piridazina, pirimidina, pirazina, triazina y similares; anillos heterocíclicos aromáticos fusionados de 8 a 12 miembros tales como benzofurano, isobenzofurano, benzo[b]tiofeno, indol, isoindol, 1H-indazol, bencimidazol, benzoxazol, 1.,2-benzisoxazol, benzotiazol, benzopyrane, 1,2-benzisotiazol, 1H-benzotriazol, quinolina, isoquinolina, cinolina, quinazolina, quinoxalina, ftalazina, naftiridina, purina, pteridina, carbazol, α-carbolina, y β-carbolina, γ-carbolina, acridina, fenoxazina, fenotiazina, fenazina, fenoxatiina, tiantreno, fenantridina, fenantrolina, indolizina, pirrolo[1,2-b]piridazina, prazolo[1,5-a]piridina, imidazo[1,2-a]piridina, imidazo[1,5-a]piridina, imidazo[1,2-b]piridazina, imidazo[1,2-a]pirimidina, 1,2,4-triazolo[4,3-a]piridina, 1,2,4-triazolo[4,3-b]piridazina y similares (preferiblemente un anillo heterocíclico en el cual el anillo heterocíclico aromático monocíclico de 5 a 6 miembros antes mencionado es fusionado con un anillo de benceno, o un anillo

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heterocíclico en el cual los mismos o diferentes dos de los anillos heterocíclicos aromáticos monocíclicos de 5 a 6 miembros antes mencionados son fusionados, muy preferiblemente un anillo heterocíclico en el cual el anillo heterocíclico aromático monocíclico de 5 a 6 miembros antes mencionado es fusionado con un anillo de benceno) y similares.

El anillo C es preferiblemente un anillo heterocíclico aromático monocíclico, un anillo de benceno o similar, y entre otros, se prefiere un anillo heterocíclico aromático monocíclico de 5 miembros tal como pirazol, imidazol, tiazol, oxazol, isoxazol, 1,2,4-oxadiazol, 1,3,4-oxadiazol o similar.

Aunque el anillo C puede ser un anillo aromático que tiene un átomo de hidrógeno que puede ser desprotonado o un anillo aromático que no tiene átomo de hidrógeno que puede ser desprotonado, un anillo aromático que no tiene átomo de hidrógeno que puede ser desprotonado es preferido. El anillo aromático que no tiene átomo de hidrógeno que puede ser desprotonado incluye, además de un anillo aromático que originalmente no tiene átomo de hidrógeno que puede ser desprotonado (v.gr., anillo de benceno, tiazol, oxazol, isoxazol, 1,2,4-oxadiazol, 1,3,4-oxadiazol, etc.), un anillo aromático en el cual un átomo de hidrógeno que puede ser desprotonado es sustituido (v.gr., pirrol, pirazol, imidazol,

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etc., cuyo átomo de hidrógeno en el átomo de nitrógeno que constituye el anillo es sustituido o que está unido a X^{1a} o/y X^{1b} por medio del átomo de nitrógeno que constituye el anillo).

El sustituyente, cuyo anillo aromático del "anillo aromático opcionalmente sustituido adicional" representado por el anillo C puede tener, incluye (i) un grupo carboxilo opcionalmente esterificado con un grupo alquilo de C_{1-6} opcionalmente halogenado o un grupo arilo de C_{6-10}-alquilo de C_{1-4} opcionalmente halogenado (v.gr., metilo, etilo, propilo, isopropilo, butilo, ter-butilo, fenilo, bencilo, etc.), (ii) un grupo ácido fosfórico opcionalmente mono- o di-sustituido con alquilo de C_{1-6} opcionalmente halogenado (v.gr., metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, n-pentilo, isopentilo, neopentilo, hexilo, etc.) o alcanoiloxi de C_{2-7}-alquilo de C_{1-6} tal como o pivaloiloximetilo, (iii) un grupo ácido sulfónico, (iv) un grupo sulfonamida opcionalmente sustituido con un grupo alquilo de C_{1-6} opcionalmente halogenado o un grupo arilo de C_{6-10}-alquilo de C_{1-4} opcionalmente halogenado (v.gr., metilo, etilo, propilo, isopropilo, butilo, ter-butilo, bencilo, etc.), (v) un grupo hidroxilo y un grupo sulfhidrilo, que puede ser opcionalmente sustituido con un grupo alquilo de C_{1-3} opcionalmente halogenado (v.gr., metilo, etilo, propilo, etc.), (vi) un grupo carbamoilo, (vii) un grupo fenilo

opcionalmente sustituido con 1 a 5 sustituyentes [v.gr., grupo hidroxilo, cloro, flúor, grupo aminosulfonilo, grupo amino opcionalmente sustituido con grupo alquilo de C_{1-3} (v.gr., metilo, etilo, propilo, etc.)] y opcionalmente unido al anillo aromático por medio de O o S, (viii) un grupo amino opcionalmente mono- o di-sustituido con un grupo alquilo de C_{1-3} opcionalmente halogenado (v.gr., metilo, etilo, propilo, etc.), (ix) un grupo amino cíclico opcionalmente sustituido con 1 a 3 alquilo de C_{1-3} (v.gr., metilo, etilo, etc.), bencilo, fenilo y similares (v.gr., un grupo amino cíclico de 5 a 6 miembros que contiene opcionalmente un átomo de oxígeno o un átomo de azufre además de átomos de nitrógeno como átomos constituyentes de anillo, tales como un grupo amino cíclico derivado (al remover un átomo de hidrógeno) de amina cíclica tal como piperidina, pirrolidina, morfolina, tiomorfolina, piperazina, 4-metilpiperazina, 4-bencilpiperazina, 4-fenilpiperazina, 1,2,3,4-tetrahidroisoquinolina o ftalimida), (x) un grupo heterocíclico aromático de 5 a 6 miembros que contiene 1 a 4 heteroátomos seleccionados de N, O y S y opcionalmente unido al anillo aromático por medio de O o S (v.gr., piridilo, imidazolilo, indolilo, tetrazolilo, etc.), (xi) un átomo de halógeno (v.gr., cloro, flúor, bromo, yodo, etc.), (xii) un grupo alquilo de C_{1-4} (v.gr., metilo, etilo, propilo, isopropilo, butilo, ter-butilo, etc.), un grupo alcoxi de C_{1-4}

(v.gr., metoxi, etoxi, propoxi, isopropoxi, butoxi, ter-butoxi, etc.) o un grupo alquiltio de C_{1-4} (v.gr., metiltio, etiltio, propiltio, isopropiltio, butiltio, ter-butiltio etc.), cada uno de los cuales puede ser opcionalmente sustituido con un sustituyente seleccionado de un átomo de halógeno, un grupo alcoxi de C_{1-4}, un grupo alquiltio de C_{1-4}, carboxilo y fenilo, (xiii) un grupo cicloalquilo de C_{5-7} (v.gr., ciclopentilo, ciclohexilo, cicloheptilo, etc.), y (xiv) alcanoiloxi de C_{1-7} opcionalmente halogenado (v.gr., formiloxi, acetoxi, propioniloxi, butiriloxi, ter-butoxicarboniloxi, isobutiriloxi, valeriloxi, pivaloiloxi, etc.). El "anillo aromático opcionalmente sustituido adicional" puede ser sustituido con 1 a 6, preferiblemente 1 a 3 de esos sustituyentes en posiciones sustituibles. Dos de esos sustituyentes se pueden tomar juntos para formar alquileno de C_{3-6}, alquilenoxi de C_{3-6}, alquilenodioxi de C_{3-6} o similar. Por ejemplo, cuando dos sustituyentes adyacentes en un grupo fenilo están ligados uno a otro para formar alquileno de C_4, se forma un grupo tetrahidronaftilo.

El grupo alquilo inferior del "grupo alquilo inferior opcionalmente sustituido con un grupo hidroxilo opcionalmente sustituido" representado por R^1 incluye, por ejemplo, alquilo de C_{1-6} tal como metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, n-pentilo, isopentilo, neopentilo, hexilo y similares. Entre ellos, un grupo alquilo

de C_{3-6} es preferido y un grupo alquilo de C_{4-5} es más preferido. Entre otros, un grupo alquilo de C_{4-5} ramificado tal como isobutilo, neopentilo o similar es preferido.

El sustituyente, cuyo grupo alquilo inferior del "grupo alquilo inferior opcionalmente sustituido con un grupo hidroxilo opcionalmente sustituido" representado por R^1 puede tener, incluye un grupo hidroxilo opcionalmente sustituido con alcanoilo de C_{2-20} o alquilo de C_{1-7}. Ese sustituyente incluye, por ejemplo, un grupo hidroxilo, acetiloxi (acetoxi), propioniloxi, ter-butoxicarboniloxi, palmitoiloxi, dimetilaminoacetiloxi, 2-aminopropioniloxi y similares. El grupo alquilo inferior puede ser sustituido con 1-3 de esos sustituyentes en posiciones sustituibles.

Ejemplos de R^1 incluye 1-propilo, 1-isopropilo, 1-isobutilo, 1-neopentilo, 2,2-dimetil-3-hidroxipropilo, 3-hidroxi-2-hidroximetil-2-metilpropilo, 3-acetoxi-2,2-dimetilpropilo, 3-acetoxi-2-hidroximetil-2-metil-propilo, 3-acetoxi-2-acetoximetil-2-metilpropilo, [1-(hidroximetil)-ciclobutil]metilo y similares. Entre ellos, se prefieren 2,2-dimetil-3-hidroxipropilo, 3-hidroxi-2-hidroximetil-2-metilpropilo, 3-acetoxi-2,2-dimetilpropilo, 3-acetoxi-2-hidroximetil-2-metilpropilo, 3-acetoxi-2-acetoximetil-2-metilpropilo y similares.

El alquileno inferior del "alquileno inferior opcionalmente sustituido" representado por X^{1a} incluye, por

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ejemplo, alquileno de C_{1-6} tal como metileno, dimetileno, trimetileno, tetrametileno, pentametileno, hexametileno y similares. Entre ellos, se prefiere alquileno de C_{1-4} de cadena recta tal como metileno, dimetileno, trimetileno, tetrametileno o similar, y más preferido es alquileno de C_{1-3} de cadena recta.

El sustituyente, cuyo alquileno inferior del "alquileno inferior opcionalmente sustituido" representado por X^{1a} puede tener, incluye los mismos grupos que aquellos ilustrados anteriormente como el sustituyente, que el anillo aromático del "anillo aromático opcionalmente sustituido adicional" representado por el anillo C puede tener, un grupo oxo y similares. El "alquileno inferior" puede ser sustituido con 1 a 6, preferiblemente 1 a 3 de esos sustituyentes en posiciones sustituibles.

X^{1a} es preferiblemente un enlace o alquileno de C_{1-3} de cadena recta, y en particular preferiblemente metileno.

El alquileno inferior del "alquileno inferior opcionalmente sustituido" representado por X^{1b} incluye los mismos grupos que aquellos ilustrados como el alquileno inferior del "alquileno inferior opcionalmente sustituido" representado por X^{1a}. El sustituyente, que el alquileno inferior del "alquileno inferior opcionalmente sustituido" representado por X^{1b} puede tener, incluye el mismo número de los mismos grupos que aquellos ilustrados como el

sustituyente que el alquileno inferior del "alquileno inferior opcionalmente sustituido" representado por X^{1a} puede tener.

X^{1b} es preferiblemente un enlace o alquileno de C_{1-3} de cadena recta, y en particular preferiblemente un enlace.

X^2 es preferiblemente un enlace.

El "grupo hidrocarburo divalente" del "grupo hidrocarburo divalente opcionalmente sustituido" representado por X^3 incluye un grupo formado al remover un átomo de hidrógeno de un grupo hidrocarburo. El grupo hidrocarburo incluye un grupo alquilo de cadena recta o ramificada de C_{1-7} (v.gr., metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, 1,1-dimetiletilo, n-pentilo, 3-metilbutilo, 2-metilbutilo, 1-metilbutilo, 1-etilpropilo, n-hexilo, 4-metilpentilo, 3-metilpentilo, 2-metilpentilo, 2-etilbutilo, 1-etilbutilo, neopentilo, hexilo, heptilo), un grupo cicloalquilo de C_{3-7} (ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclohexilmetilo, etc.), un grupo alquenilo de C_{2-6} de cadena recta o ramificada (v.gr., vinilo, alilo, isopropenilo, 2-metilalilo, 1-propenilo, 2-metil-1-propenilo, 2-metil-2-propenilo, 1-butenilo, 2-butenilo, 3-butenilo, 2-etil-1-butenilo, 2-metil-2-butenilo, 3-metil-2-butenilo, 1-pentenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo, 4-metil-3-pentenilo, 1-hexenilo, 2-hexenilo, 3-hexenilo, 4-hexenilo, 5-hexenilo, etc.), un grupo arilo de C_{6-10} (v.gr., fenilo,

naftilo), un grupo arilalquilo de C_{7-14} (v.gr., bencilo, fenetilo, naftilmetilo) y similares.

El sustituyente, cuyo "grupo hidrocarburo divalente" del "grupo hidrocarburo divalente opcionalmente sustituido" representado por X^3 puede tener, incluye el mismo grupo que aquellos ilustrados anteriormente como el sustituyente que el alquileno inferior del "alquileno inferior opcionalmente sustituido" representado por X^{1a} puede tener, alquilideno de C_{1-6} opcionalmente halogenado (v.gr., metilideno, etilideno, propilideno, isopropilideno, butenilideno, etc.), vinilideno, ciclohexilideno, bencilideno y similares. El "grupo hidrocarburo divalente" puede ser sustituido con 1 a 6, preferiblemente 1 a 3 de esos sustituyentes en posiciones sustituibles.

El "grupo hidrocarburo divalente" del "grupo hidrocarburo divalente opcionalmente sustituido" representado por X^3 preferiblemente incluye (1) alquileno de cadena recta o ramificada en el cual el número de átomos de carbono que constituyen la parte de cadena recta es 1 a 7 (preferiblemente 1 a 4) (v.gr., metileno, etileno, trimetileno, tetrametileno, pentametileno, hexametileno, heptametileno, propileno, etilmetileno, etiletileno, propiletileno, butiletileno, metiltetrametileno, metiltrimetileno, etc.), (2) un doble enlace - que contiene cadena de carbono en el cual el número de átomos de carbono

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que constituyen la parte de cadena recta es 2 a 7 (preferiblemente 2 a 4) (v.gr., vinileno, propenileno, butenileno, butadienileno, metilpropenileno, etilpropenileno, propilpropenileno, metilbutenileno, etilbutenileno, propilbutenileno, metilbutadienileno, etilbutadienileno, propilbutadienileno, pentenileno, hexenileno, heptenileno, pentadienileno, hexadienileno, heptadienileno, etc.), (3) fenileno (v.gr., 1,2-fenileno, 1,3-fenileno, 1,4-fenileno, etc.) y (4) un grupo divalente en el cual el fenileno y alquileno y/o alquenileno se combinan (v.gr., $-CH_2-C_6H_4-$, $-CH_2CH_2-C_6H_4-$, $-CH_2-C_6H_4-CH_2-$ etc.).

X^3 es preferiblemente alquileno de C_{1-4} tal como metileno, etileno, trimetileno, tetrametileno o similar, vinileno, propenileno, fenileno o similar.

El "grupo carboxilo opcionalmente esterificado o amidado" representado por Y incluye carboxilo, alcoxicarbonilo inferior que tiene 2 a 7 átomos de carbono (v.gr., metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, isopropoxicarbonilo, butoxicarbonilo, ter-butoxicarbonilo, sec-butoxicarbonilo, pentiloxicarbonilo, isopentiloxi-carbonilo, neopentiloxicarbonilo, etc.), ariloxicarbonilo de C_{7-14} (v.gr., fenoxicarbonilo, 1-naftoxicarbonilo), aralquiloxicarbonilo de C_{8-12} (v.gr., benciloxicarbonilo, etc.), carbamoilo, N-alquilcarbamoilo de C_{1-6}, N,N-dialquilcarbamoilo de C_{1-6}, N-aralquilcarbamoilo de C_{8-12}, N,N-diaralquilcarbamoilo de C_{8-12}, 1-pirrolidinilcarbonilo,

piperidinocarbonilo, morfolinocarbonilo y similares. Entre ellos, Y es preferiblemente carboxilo, metoxicarbonilo, etoxicarbonilo o similar, y en particular preferiblemente carboxilo.

El compuesto representado por la fórmula [1] incluye, en particular preferiblemente, ácido 3-(2-{3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]propil}-1,3-tiazol-5-il)propiónico, ácido 3-(2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,3-tiazol-4-il)propiónico, ácido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)propiónico, ácido 2-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil}-1-isobutil-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)acético, ácido 5-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)pentanoico, ácido 5-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)pentanoico, ácido 5-(3-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-

il]metil}-1,2,4-oxodiazol-5-il)pentanoico y similares.

El compuesto representado por la fórmula [I] puede estar en forma libre o una forma de sal farmacológicamente aceptable, y ambas formas se incluyen en el alcance de la presente invención. Cuando el compuesto representado por la fórmula [I] tiene un grupo ácido tal como un grupo carboxilo, etc., el compuesto puede formar una sal con bases inorgánicas (v.gr., metal alcalino tal como sodio, potasio, etc., metal alcalinotérreo tal como calcio, magnesio, etc., metal de transición tal como zinc, hierro, cobre, etc.) o bases orgánicas (v.gr., aminas orgánicas tales como trimetilamina, trietilamina, piridina, picolina, etanolamina, dietanolamina, trietanolamina, tris(hidroximetil)metilamina, diciclohexilamina, N,N'-dibenciletilendiamina y t-butilamina, aminoácidos básicos tales como arginina, lisina, ornitina, y similares).

Cuando el compuesto representado por la fórmula [I] de la presente invención tiene un grupo básico tal como un grupo amino o similar, el compuesto puede formar una sal con ácidos inorgánicos o ácidos orgánicos (v.gr., ácido clorhídrico, ácido nítrico, ácido sulfúrico, ácido fosfórico, ácido carbónico, ácido bicarbónico, ácido fórmico, ácido acético, ácido propiónico, ácido trifluoroacético, ácido fumárico, ácido oxálico, ácido tartárico, ácido maleico, ácido cítrico, ácido succínico, ácido málico, ácido

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metansulfónico, ácido bencensulfónico, ácido P-toluensulfónico, etc.) o aminoácidos ácidos tal como ácido aspártico o ácido glutámico.

El compuesto representado por la fórmula [I] o una sal del mismo tiene átomos de carbono asimétricos en la posición 3 y la posición 5, y puede ser una mezcla de estereoisómeros. Los isómeros pueden ser separados por un medio conocido. Se prefiere la forma trans en la cual los sustituyentes a la posición 3 y la posición 5 son dirigidos a la dirección opuesta unos a otros en relación con el plano del anillo de 7 miembros, y específicamente preferido es un compuesto que tiene la configuración absoluta representada por la fórmula [Ia]. Además, el compuesto representado por la fórmula [I] o una sal del mismo puede ser una forma racémica o una forma ópticamente activa, y la forma ópticamente activa puede separarse de la forma racémica por un medio de resolución óptica conocido.

Un profármaco del compuesto representado por la fórmula [I] o una sal del mismo se refiere a un compuesto que es convertido al compuesto representado por la fórmula [I] o una sal del mismo por una reacción con una enzima o ácido gástrico bajo la condición fisiológica *in vivo*, es decir, un compuesto que es cambiado al compuesto representado por la fórmula [I] o una sal del mismo por oxidación enzimática, reducción, hidrólisis o similar, o un compuesto que es

cambiado al compuesto representado por la fórmula [I] o una sal del mismo por hidrólisis con ácido gástrico o similar. El profármaco del compuesto representado por la fórmula [I] o una sal del mismo incluye, cuando el compuesto representado por la fórmula [I] o una sal del mismo tiene un grupo amino, un compuesto cuyo grupo amino es acilado, alquilado o fosforilado (v.gr., el compuesto representado por la fórmula [I] o una sal del mismo cuyo grupo amino es eicosanoilado, alanilado, pentilaminocarbonilado, (5-metil-2-oxo-1,3-dioxolen-4-il)metoxicarbonilado, tetrahidrofuranilado, pirrolidilmetilado, pivaloiloximetilado o ter-butilado, etc.); cuando el compuesto representado por la fórmula [I] o una sal del mismo tiene un grupo hidroxilo, un compuesto cuyo grupo hidroxilo es acilado, alquilado, fosforilado o borado (v.gr., un compuesto cuyo grupo hidroxilo es acetilado, palmitoilado, propanoilado, pivaloilado, succinilado, furnarilado, alanilado o dimetilaminometilcarbonilado, etc.); y cuando el compuesto representado por la fórmula [I] o una sal del mismo tiene un grupo carboxilo, un compuesto cuyo grupo carboxilo es esterificado o amidado (v.gr., un compuesto cuyo grupo carboxilo es etilesterificado, fenilesterificado, carboximetilesterificado, dimetilamino-metilesterificado, pivaloiloximetilesterificado, etoxicarboniloxietilesterificado, ftalidilesterificado, (5-metil-2-oxo-1,3-dioxolen-4-il)metilesterificado,

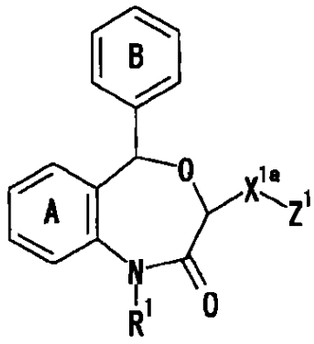
ciclohexiloxicarboniletilesterificado o metilamidado, etc.). Estos profármacos se pueden preparar a partir del compuesto representado por la fórmula [I] o una sal del mismo por un método conocido *per se*.

Un profármaco del compuesto representado por la fórmula [I] o una sal del mismo puede ser un compuesto que es cambiado al compuesto representado por la fórmula [I] o una sal del mismo bajo la condición fisiológica como se describe en Development of Pharmaceutical Products, vol. 7, Molecular Design, 163-198, Hirokawa Shoten (1990).

El compuesto representado por la fórmula [I] o una sal del mismo puede ser hidra o anhidra.

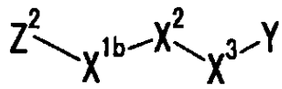
El compuesto representado por la fórmula [I] o una sal del mismo puede ser marcado con un isótopo (v.gr., ^{3}H, ^{14}C, ^{35}S, ^{125}I etc.).

El compuesto representado por la fórmula [I] o una sal del mismo se puede preparar, por ejemplo, al hacer reaccionar un compuesto representado por la fórmula [II]:



en donde los símbolos son como se definió antes, o

un derivado del mismo con un compuesto representado por la fórmula:



en donde los símbolos son como se definió antes, o una sal del mismo de conformidad con un método conocido *per se* (v.gr., "Comprehensive Heterocyclic Chemistry", ed. de A.R. Katritzky y C.W.Rees, vol.4-6, Pergamon Press, Oxford, 1984), o posteriormente al formar un anillo heterocíclico aromático por reacción de ciclización.

Una combinación del "grupo funcional implicado en una reacción formadora de anillo heterocíclico aromático" representado por Z^1 y Z^2 incluye, por ejemplo:

(1) uno es un grupo carboxilo y el otro es un grupo 2-aminoalcanoilo,

(2) uno es un grupo carboxilo y el otro es hidrazida,

(3) uno es un grupo tiocarbamoilo y el otro es un grupo alcanoilo sustituido con un átomo de halógeno en la posición 2, y

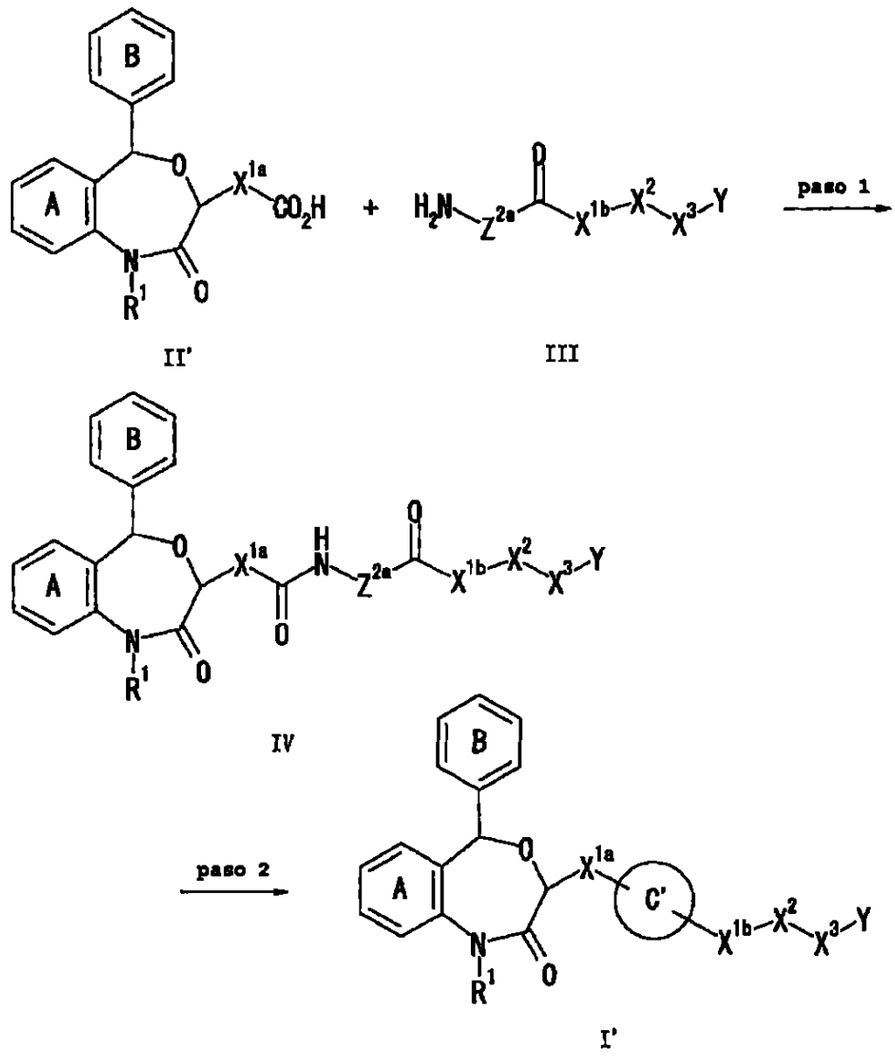
(4) uno es un grupo N-hidroxiamidino y el otro es halogenuro de ácido carboxílico, o similar.

Un método de preparación del compuesto representado por la fórmula [I'] incluye el procedimiento A, el procedimiento B y similares, en donde un compuesto

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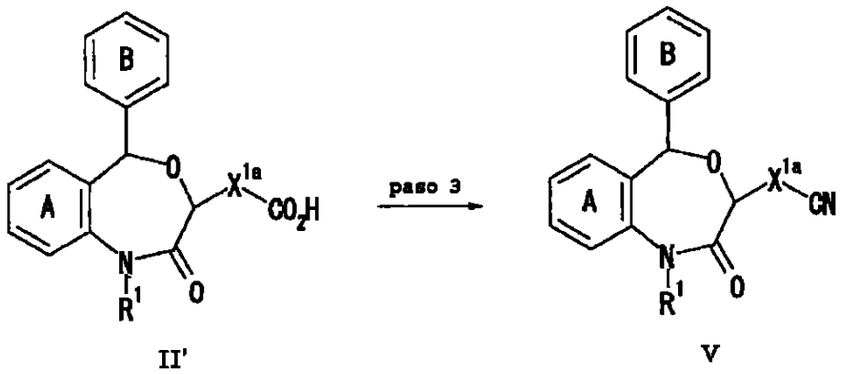
representado por la fórmula [II'] o un derivado del mismo se usa como el material de partida.

Procedimiento A

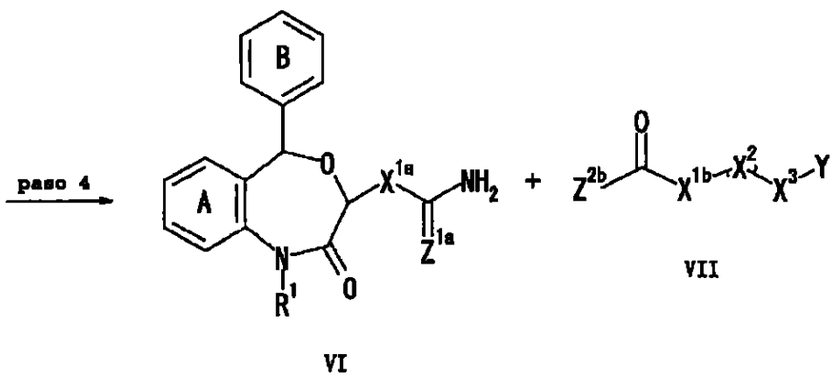


I'

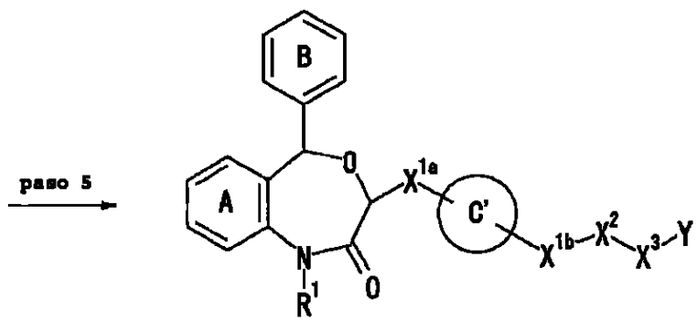
Procedimiento B



II' V



VI VII



I'

en donde, Z^{1a} representa un grupo hidroxiimino o un átomo de azufre, Z^{2a} representa un grupo metileno o un grupo imino, y Z^{2b} representa un átomo de halógeno, o un grupo alquilo inferior en el cual el átomo de carbono adyacente al grupo carbonilo es sustituido con un átomo de halógeno.

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En el paso 1, un método de preparación del compuesto representado por la fórmula [IV] del compuesto representado por la fórmula [II'] o un derivado del mismo y el compuesto representado por la fórmula [III] incluye, por ejemplo, un método que comprende condensar el compuesto representado por la fórmula [II'] y el compuesto representado por la fórmula [111] con un agente condensador de deshidratación generalmente conocido en presencia de ambos compuestos simultáneamente, un método que comprende activar el ácido carboxílico del compuesto representado por la fórmula [II'] por un método de activación generalmente conocido y después hacerlo reaccionar con el compuesto representado por la fórmula [III], y un método que comprende hacer reaccionar un derivado del compuesto representado por la fórmula [II'] con el compuesto representado por la fórmula [III]. El agente condensador de deshidratación incluye, por ejemplo, N,N'-diciclohexilcarbodiimida, 1-etil-3-(3-dimetilaminopropil)carbodiimida, carbonildiimidazol, hexafluorofosfato de 1H-benzotriazol-1-iloxitris(dimetil-amino)fosfonio y similares.

Un método de activación de ácido carboxílico incluye, por ejemplo, un método que comprende convertir ácido carboxílico en anhídrido ácido con cloroformiato, cloruro de pivaloilo o similar, un método que comprende convertir ácido carboxílico en cloruro ácido con cloruro de oxalilo, cloruro

96-30.886
96-46.405

de tionilo o similar, el método comprende esterificar ácido carboxílico con 1-hidroxibenzotriazol con el uso de un agente condensador de deshidratación o similar, y similares.

Un método de reacción de un derivado del compuesto representado por la fórmula [II'] con el compuesto representado por la fórmula [III] incluye un método que comprende calentar un derivado de éster del compuesto representado por la fórmula [II'] en presencia del compuesto representado por la fórmula [III].

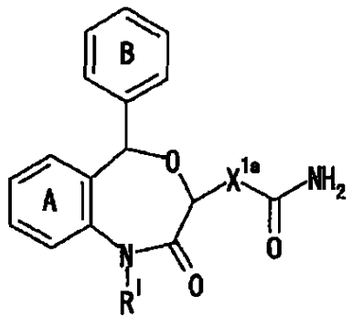
El compuesto representado por la fórmula [III] se puede preparar, por ejemplo, de conformidad con síntesis conveniente de ácido 3-aminolevulínico, Ayelet Nudelman y Abraham Nodelman, Synthesis 1999, No.4, pp 568-570.

En el paso 2, un método de preparación del compuesto representado por la fórmula [I] del compuesto representado por la fórmula [IV] incluye un método que comprende tratamiento con reactivo de Lawesson u oxicloruro de fósforo ($POCl_3$).

En el paso 3, un método de preparación del compuesto representado por la fórmula [V] del compuesto representado por la fórmula [II'] o un derivado del mismo incluye, por ejemplo:

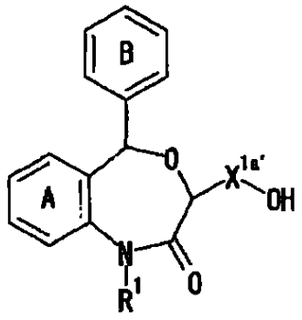
1) un método de preparación del compuesto representado por la fórmula [V] con el uso de, como un intermediario, un compuesto representado por la fórmula

[VIII]:



obtenido del compuesto representado por la fórmula [II'] por un método de amidación generalmente conocido;

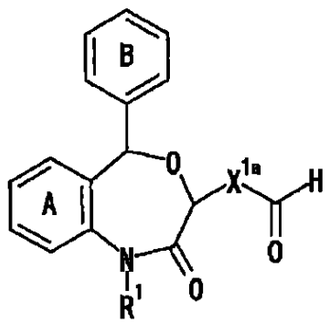
2) un método de preparación del compuesto representado por la fórmula [V] con el uso de, como un intermediario, un compuesto representado por la fórmula [IX]:



en donde $X^{1a'}$ representa un alquileno inferior opcionalmente sustituido, obtenido por una reacción de reducción de ácido carboxílico o un derivado del mismo del compuesto representado por la fórmula [II'] o un derivado del mismo;

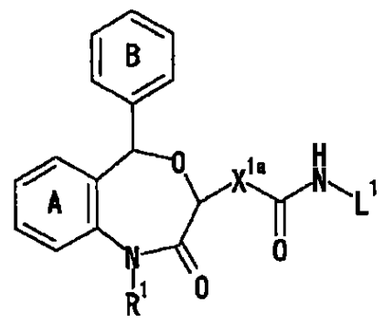
3) un método de preparación del compuesto representado por la fórmula [V} con el uso de, como un

intermediario, un compuesto representado por la fórmula [X]:



obtenido por una reacción de reducción generalmente conocida de ácido carboxílico o un derivado del mismo del compuesto representado por la fórmula [II'] o un derivado del mismo, o por una reacción de oxidación generalmente conocida de alcohol del compuesto representado por la fórmula [IX]; o similar.

Un método de amidación incluye un método que comprende condensación con amoniaco o 1-hidroxibenzotriazol-amoniaco (HOBt-NH_3) con el uso de un agente de condensación por deshidratación y un método que comprende la preparación de amida representada por la fórmula [XI]:



en donde L^1 representa un grupo protector para un

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grupo amino, seguido por remoción del grupo protector para un grupo amino.

Una reacción de reducción de ácido carboxílico o un derivado del mismo incluye una reacción de reducción de ácido carboxílico o un derivado de ácido carboxílico con el uso de un agente reductor tal como hidruro de litio-aluminio, hidruro de diisobutilaluminio, borhidruro de sodio, o similar.

Una reacción de oxidación de alcohol incluye, por ejemplo, un método que comprende tratamiento con un complejo de trióxido de azufre-piridina o cloruro de oxalilo en sulfuro de dimetilo, un método de oxidación que usa un agente oxidante tal como clorocromato de piridinio o reactivo de Dess-Martin, etc., y similares.

Un método de preparación del compuesto representado por la fórmula [V] del compuesto representado por la fórmula [VIII] incluye, por ejemplo, un método que comprende tratamiento con anhídrido tal como anhídrido de ácido trifluorometansulfónico, un método que comprende tratamiento con un agente de condensación por deshidratación tal como carbonildiimidazol en presencia de bromuro de alilo y similares.

Un método de preparación del compuesto representado por la fórmula [V] del compuesto representado por la fórmula [IX] incluye, por ejemplo, un método que comprende conversión

del grupo hidroxilo en un grupo sustituible seguido por tratamiento con cianuro, un método que comprende reacción de Mitsunobu en presencia de cianuro tal como acetona-cianohidrina (un método que comprende tratamiento con un ácido azodicarboxílico derivado tal como 1,1'-(azodicarbonil)dipiperidina y un compuesto de fósforo orgánico tal como tri-n-butilfosfina o trifenilfosfina) y similares.

Un método de preparación del compuesto representado por la fórmula [V] del compuesto representado por la fórmula [X] incluye, por ejemplo, un método que comprende reacción con un agente oxidante tal como yodo en amoniaco acuoso, un método que comprende reacción de Wittig con éster de ácido fosfórico que contiene un grupo ciano en su molécula tal como éster dietílico de ácido cianometilfosfórico seguido por reacción de hidrogenación y similares.

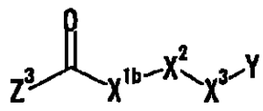
En el paso 4, un método de preparación del compuesto representado por la fórmula [VI] del compuesto representado por la fórmula [V] incluye, por ejemplo, un método que comprende tratamiento del compuesto representado por la fórmula [V] con éster dietílico de ácido ditiofosfórico o similar, un método que comprende tratamiento con cloruro de hidroxilamonio en presencia de un álcali tal como bicarbonato de sodio.

Además, un método de preparación del compuesto

representado por la fórmula [VI] incluye, por ejemplo, un método que comprende tratamiento del compuesto representado por la fórmula [VIII] con un agente sulfurizante tal como pentafluoruro de difósforo y similares.

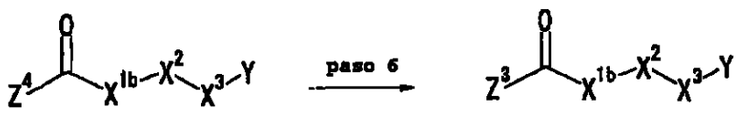
En el paso 5, un método de preparación del compuesto representado por la fórmula [I] del compuesto representado por la fórmula [VI] y el compuesto representado por la fórmula [VII] incluye, por ejemplo, un método que comprende calentar el compuesto representado por la fórmula [VI] en presencia del compuesto representado por la fórmula [VII] y similares.

Entre los compuestos representados por la fórmula [VII], un compuesto representado por la fórmula [XII]:



en donde Z^3 representa un grupo alquilo inferior en el cual es sustituido con un átomo de halógeno en el átomo de carbono adyacente al grupo carbonilo, se puede preparar, por ejemplo, por el procedimiento C o similar.

Procedimiento C



XIII XII

en donde Z^4 representa un átomo de halógeno.

En el paso 6, un método de preparación del compuesto representado por la fórmula [XII] del compuesto representado por la fórmula [XIII] incluye, por ejemplo, un método que comprende la reacción con diazometano o trimetilsilildiazometano en una solución de ácido bromhídrico en ácido acético y similares.

En cada reacción del procedimiento para preparar el compuesto [I] o una sal del mismo y cada reacción para síntesis de los compuestos de partida anteriormente descritos, cuando el compuesto de partida tiene un grupo amino, un grupo carboxilo o un grupo hidroxi como un sustituyente, ese sustituyente puede ser protegido con un grupo protector que usualmente se usa en química de péptidos o similar. Después de la reacción, si es necesario, el grupo protector puede ser removido para obtener el compuesto deseado.

Un grupo protector para un grupo amino incluye, por ejemplo, formilo, alquilcarbonilo de C_{1-6} (v.gr., acetilo, etilcarbonilo, etc.), fenilcarbonilo, alquilo de C_{1-6}-oxicarbonilo (v.gr., metoxicarbonilo, etoxicarbonilo, etc.), feniloxicarbonilo, alquilo de C_{7-10}-carbonilo (v.gr., bencilcarbonilo etc.), tritilo, ftaloilo, N,N-dimetilaminometileno y similares, cada uno de los cuales puede ser opcionalmente sustituido. Tal como un sustituyente,

un átomo de halógeno (v.gr., flúor, cloro, bromo, yodo etc.), alquilo de C_{1-6}-carbonilo (v.gr., metilcarbonilo, etilcarbonilo, butilcarbonilo, etc.), un grupo nitro o similar se usa y el número de sustituyentes es de aproximadamente 1 a 3.

Un grupo protector para un grupo carboxilo incluye, por ejemplo, alquilo de C_{1-6} (v.gr., metilo, etilo, n-propilo, i-propilo, n-butilo, ter-butilo, etc.), fenilo, tritilo, sililo y similares, cada uno de los cuales puede ser opcionalmente sustituido. Como sustituyente, se usa un átomo de halógeno (v.gr., flúor, cloro, bromo, yodo etc.), formilo, alquilo de C_{1-6}-carbonilo (v.gr., acetilo, etilcarbonilo, butilcarbonilo, etc.), un grupo nitro o similar y el número de sustituyentes es de aproximadamente 1 a 3.

Un grupo protector para un grupo hidroxi incluye, por ejemplo, alquilo de C_{1-6} (v.gr., metilo, etilo, n-propilo, i-propilo, n-butilo, ter-butilo, etc.), fenilo, aralquilo de C_{7-10} (v.gr., bencilo, etc.), formilo, alquilo de C_{1-6}-carbonilo (v.gr., acetilo, etilcarbonilo, etc.), feniloxicarbonilo, benzoilo, aralquilo de C_{7-10}-carbonilo (v.gr., bencilcarbonilo etc.), piranilo, furanilo, sililo y similares, cada uno de los cuales puede ser opcionalmente sustituido. Como sustituyente, se usa un átomo de halógeno (v.gr., flúor, cloro, bromo, yodo, etc.), alquilo de C_{1-6} (v.gr., metilo, etilo, n-propilo, etc.), fenilo, aralquilo de

C_{7-10} (v.gr., bencilo, etc.), un grupo nitro o similar y el número de sustituyentes es de aproximadamente 1 a 4.

Un método de remoción de un grupo protector puede ser un método conocido *per se* o el método similar, y por ejemplo, se usa un método que comprende tratamiento con ácido, base, reducción, luz ultravioleta, hidrazina, fenilhidrazina, N-metilditiocarbamato de sodio, fluoruro de tetrabutilamonio, acetato de paladio o similar.

Además, en cada reacción del procedimiento para preparar el compuesto [I] o una sal del mismo y cada reacción para sintetizar los compuestos de partida anteriormente descritos, un solvente generalmente conocido se puede usar durante la reacción.

Un solvente generalmente conocido incluye, por ejemplo, éteres tales como tetrahidrofurano, éter dietílico, 1,2-dimetoxietano y 1,4-dioxano; ésteres tales como acetato de etilo y acetato de butilo; hidrocarburos aromáticos tales como benceno y tolueno; compuestos heterocíclicos aromáticos tales como piridina y lutidina; amidas tales como N,N-dimetilformamida y N-metilpirrolidona; halogenuros tales como cloroformo y cloruro de metileno; alcoholes tales como metanol, etanol, 2-propanol y 2,2-dimetiletanol; compuestos de hidrocarburo tales como hexano, heptano y éter de petróleo; ácidos carboxílicos tales como ácido fórmico y ácido acético; agua; y similares.

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Un solvente usado en la reacción puede ser un solvente individual o una mezcla de 2 a 6 solventes.

La reacción también se puede llevar a cabo en presencia de una base tal como aminas tales como trietilamina, N,N-diisopropilamina, piridina o N-metilmorfolina, hidróxido de sodio, carbonato de potasio o similar.

La reacción también se puede llevar a cabo en presencia de un ácido tal como ácido clorhídrico, ácido sulfúrico, ácido acético o similar.

El compuesto representado por la fórmula [I] o una sal del mismo obtenido por los métodos anteriores se puede aislar o purificar por un medio de separación convencional tal como recristalización, destilación, cromatografía o similar. Cuando el compuesto representado por la fórmula [I] de la presente invención así obtenido está en forma libre, puede ser convertido a forma de sal por un método conocido *per se* o método similar (v.gr., neutralización, etc.). Por el contrario, cuando el compuesto se obtiene como una sal, puede ser convertido a la forma libre u otra sal por un método conocido *per se* o método similar. Cuando el compuesto resultante está en forma racémica, puede ser separado a la forma d y la forma l por un medio de resolución óptica convencional.

Los compuestos de partida del compuesto

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representado por la fórmula [I] o una sal del mismo también pueden estar en forma de sal similar a una sal del compuesto representado por la fórmula [I], pero el tipo de la sal no es en particular limitado siempre que la reacción no sea alterada.

El compuesto representado por la fórmula [II] o un derivado del mismo se puede preparar por, por ejemplo, un método descrito en EPA567026, WO95/21834 (solicitud del PCT basada en la solicitud de patente japonesa No.6-15531), EPA645377 (solicitud basada en la solicitud de patente japonesa No.6-229159), EPA645378 (solicitud basada en la solicitud de patente japonesa No.6-229160) o JP-A 9-136880, o método similar.

Puesto que el compuesto representado por la fórmula [I] o una sal o un profármaco del mismo (de aquí en adelante a veces referido simplemente como el compuesto (I), que incluye una sal del mismo y un profármaco del mismo) es de baja toxicidad y tiene actividad inhibidora de escualeno sintasa, actividad reductora de colesterol-LDL, actividad reductora de triglicéridos, actividad reductora de lípidos, actividad reductora de colesterol-no HDL y actividad elevadora del nivel de colesterol-HDL, es útil como un medicamento seguro para la prevención o tratamiento de hiperlipemia tal como hipercolesterolemia, hipertrigliceridemia o hipoHDLemia en un mamífero (v.gr.,

ratón, rata, conejo, perro, gato, ganado vacuno, res, mono, humano y similares) y también es útil para prevención o tratamiento de síndrome metabólico. Más aún, el compuesto es útil como un medicamento seguro para la prevención o tratamiento de enfermedad del riñón tal como nefritis o nefropatía, arterioesclerosis, enfermedad isquémica, infarto cardiaco, angina de pecho, insuficiencia cardiaca, aneurisma, arterioesclerosis cerebral, apoplejía cerebral, ataque isquémico transitorio, infarto cerebral, arterioesclerosis periférica, claudicación intermitente, trombosis, hipertensión, osteoporosis, diabetes (v.gr., resistencia a la insulina-tipo dependiente y similares), complicaciones diabéticas (v.gr., nefropatía diabética, neuropatía diabética, retinopatía diabética, angiopatía diabética y similares), trastorno pancreático, o restenosis después de plastia coronaria percutánea (PTCA) o colocación de stent.

De aquí en adelante la utilidad de la presente invención se explica en detalle.

El compuesto (I) tiene actividad reductora de triglicéridos y actividad reductora de colesterol superiores así como características biológicas de las mismas, y es específicamente adecuado para el tratamiento o prevención de hiperlipemia, en particular hipertriglicerıdemia, hiperlipoproteinemia e hipercolesterolemia, así como síndrome metabólico y lesión vascular aterosclerótica que surge a

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partir del mismo y enfermedad secundaria del mismo tal como enfermedad de arteria coronaria, infarto cardiaco, angina de pecho, infarto cerebral, isquemia cerebral, claudicación intermitente, arterioesclerosis periférica, gangrena y similares.

Para el tratamiento de estas enfermedades, el compuesto (I) se puede usar solo o se puede usar en combinación con otros ingredientes de fármaco tales como un agente reductor de lípidos, un agente reductor de colesterol, un agente elevador del nivel de HDL o un inhibidor de absorción de colesterol (administrado simultáneamente o administrado a cierto intervalo). En este caso, estos compuestos preferiblemente se administran como preparaciones orales (con la inclusión de tabletas desintegradoras intraoral) o se pueden administrar opcionalmente en forma de supositorio como preparaciones rectales. En este caso, los posibles ingredientes para el uso de combinación incluyen, por ejemplo, un agonista de $PPAR_{\alpha}$ tal como fibratos [v.gr., Clofibrato, Benzafibrato, Gemfibrozilo, Fenofibrato, Wy-1463, GW9578 y similares]; y un agente reductor de colesterol tal como ácido nicotínico y un derivado y análogo del mismo [v.gr., Acipimox y Probucol], una resina de unión a ácido biliar [v.gr., Colestiramina, Colestipol y similares], un compuesto

que suprime la absorción de colesterol [v.gr., Ezetimibe, Sitosterol, Neomicina y similares], un compuesto que inhibe la biosíntesis de colesterol [v.gr., un inhibidor de HMG-CoA reductasa tal como Lovastatina, Simvastatina, Pravastatina, Atorvastatina, ZD-4522 (Rosuvastatina), Itavastatina y similares], un inhibidor de escualeno epoxidasa [v.gr., NB-598 y un compuesto análogo del mismo y similares] o un agente elevador de nivel de HDL debido a inhibición de colesterol, proteína transportadora de éster [v.gr., JTT-705, CP-529-414 y similares]. Además, una combinación con un inhibidor de acil-Coenzima A colesterol aciltransferasa (ACAT) (v.gr., melinamida etc.) o un agente de regresión de placa rica en lípidos (v.gr., compuestos descritos en WO 02/06264, WO 03/059900 etc.) es posible. Además, una combinación con un agente reductor de grasa tal como un inhibidor de lipasa pancreática (v.gr.,orlistat, etc.) también es posible.

Otro posible ingrediente para el uso de combinación incluye un inhibidor de óxido escualeno-lanosterol ciclasa, por ejemplo, un derivado de decalina, un derivado de azadecalina o un derivado de indano.

En particular, al combinar con un inhibidor de HMG-CoA reductasa, mialgia y miolisis que también son el efecto colateral de un inhibidor de HMG-CoA reductasa se pueden aliviar. Además, esta combinación no sólo tiene actividad reductora de lípidos sino también es efectiva contra

osteoporosis y enfermedad de Alzheimer, y puede mejorar el pronóstico de enfermedad isquémica (apoplejía cerebral, infarto cardiaco o similar).

Además, el compuesto (I) es adecuado para tratamiento de enfermedad asociada con hipercilomicronemia, por ejemplo, pancreatitis aguda. Con respecto al mecanismo de inicio de pancreatitis, se dice que los quilomicrones causan microembolia en un vaso sanguíneo capilar pancreático, o hipercilomicronemia da por resultado un incremento en la producción de ácido graso libre por digestión de triglicérido con lipasa pancreática y después el ácido graso libre estimula fuertemente un sitio local, por lo que se desarrolla pancreatitis. Por lo tanto, puesto que el compuesto (I) tiene actividad reductora de triglicéridos, puede tratar pancreatitis y se puede usar para tratar pancreatitis solo o en combinación con una terapia conocida. Para tratamiento de esta enfermedad, el compuesto (I) se puede administrar oralmente o tópicamente y se puede usar solo o en combinación con un compuesto activo conocido. En este caso, los ingredientes que se pueden combinar incluyen, por ejemplo, aprotinin (Trasylol), gabexato mesilato (FOY), nafamostato mesilato (Fusan), citicolina (Nicoline), urinastatin (Miraclid) y similares para terapia anti-enzimática. Para el propósito de aliviar el dolor, también se usa un agente anticolinérgico, un analgésico no narcótico o un narcótico.

Un ejemplo notable adicional de aplicación del compuesto (I) es la aplicación para hiperlipemia secundaria. La enfermedad incluye diabetes, hipotiroidismo, síndrome nefrótico o insuficiencia renal crónica y similares, e inicios de hiperlipemia subsecuentes a estas enfermedades. En muchos casos, la hiperlipemia agrava estas enfermedades, a saber, forma un círculo vicioso. En vista de la actividad reductora de lípidos, el compuesto (I) es también adecuado para el tratamiento o prevención de desarrollo de estas enfermedades, y en este caso, se puede administrar solo o en combinación con los medicamentos listados a continuación.

Fármacos para tratamiento de diabetes: Kinedak, Penfil, Humalin, Euglucon, Glimicron, Daonilo, Novolin, Monotard, insulinas, Glucobay, Dimelin, Rastinon, bacilcon, Deamelin S, iszilinas; sensibilizadores de insulina (agonistas de PPAR de tiazolidina y no de tiazolidina: pioglitazona, Avandia, KRP-297, TAK-559, MCC-555 etc., fármacos de isoxazolidina: JTT-501 etc.), fármacos de biguanida (v.gr., mitiglinida, etc.), fármacos promotores de secreción de insulina (v.gr., agentes de sulfonilurea, etc.), inhibidores de α-glucocidasa (v.gr., voglibosa, etc.), β_3-

agonistas (v.gr., TAK-677 etc.), preparaciones de insulina, etc.;

Fármacos para tratamiento de hipotiroidismo: tiroides seca (Thireoid), levotiroxina sódica (Thyradin S), liotironina sódica (Thyronine, Thyronamin);

Fármacos para tratamiento de síndrome nefrótico: prednisolona (Predonine), succinato de prednisolona sódica (Predonine), succinato de metilprednisolona sódica (Solu-Medrol), betametasona (Lynderon);

Agentes para terapia con anticoagulantes: dipiridamol (Persantin), clorhidrato de dilazep (Comelian) y similares;

Fármacos para tratamiento de insuficiencia renal crónica: diuréticos [v.gr., furosemida (Lasix), bumetanida (Lunetoron), azosemida (Diart), etc.], inhibidores de ACE [v.gr., maleato de enalapril (Renivace), etc.], antagonistas de receptor de angiotensina II [v.gr., candesartan cilexetil (Blopress), losartan potásico (Nu-lotan), valsartan (Diovan), irbesartan, etc.], antagonistas de Ca (maninhiron), bloqueadores de α-receptor y similares. En combinación con estos fármacos, el compuesto (I) puede ser preferiblemente administrado oralmente.

Puesto que la hiperlipemia agrava la esclerosis arterial y causa hipertensión, el compuesto (I) es adecuado

para tratamiento o prevención de hipertensión, y en este caso, el compuesto (I) se puede administrar solo o en combinación con los medicamentos listados más adelante. En este caso, la posible combinación incluye combinaciones con, por ejemplo, antagonistas de angiotensina-II [v.gr., losartan potásico (Nu-Lotan), candesartan cilexetil (Blopress) y similares], inhibidores de ACE [v.gr., maleato de enalapril (Renivace), lisinopril (Zestrilo, Longes), clorhidrato de delapril (Adecut), captopril y similares], antagonistas de calcio [v.gr., besilato de amlodipina (Amlodin, Norvasc), clorhidrato de manidipina (Calslot) y similares], diurético hipotensivo, bloqueadores de α-receptor, bloqueadores de β-receptor y similares.

Una indicación notable adicional del compuesto (I) es osteoporosis acompañada por incremento de colesterol en la sangre. Debido a la actividad reductora de lípidos superior, el compuesto (I) se puede usar para el tratamiento o prevención de osteoporosis acompañada por incremento de colesterol en la sangre, y en este caso, el compuesto (I) se puede administrar solo o en combinación con los medicamentos listados a continuación. La posible combinación incluye combinaciones con una hormona sexual y fármacos asociados [v.gr., una preparación de estrógeno, ipriflavona (Osten), raloxifeno, osaterona, tibolona y similares], un inhibidor de

reabsorción de hueso tal como calcitoninas, preparaciones de vitamina D [v.gr., alfacalcidol, calcitriol y similares], bisfosfonatos (v.gr., etidronato, clodronato y similares) y similares, un agente acelerador de formación de hueso tal como compuesto de flúor, PTH y similares.

Otra posible aplicación del compuesto (I) es el uso para supresión de formación de trombos. Puesto que el nivel de triglicéridos en la sangre y el factor VII que está involucrado en la coagulación de la sangre tienen una correlación positiva, y el triglicérido es reducido y la coagulación es suprimida por la ingesta de ω-3 ácido graso, la hipertrigliceridemia acelera la formación de trombos. Además, puesto que el VLDL de un paciente con hiperlipemia incrementó la secreción de un inhibidor activador de plasminógeno de una célula endotelial vascular más fuertemente que el de una persona que tiene lípidos en la sangre normales, también se piensa que el triglicérido (de aquí en adelante referido como TG) reduce la capacidad de fibrinólisis. Por lo tanto, en vista de la actividad reductora de TG, el compuesto (I) es adecuado para la prevención o tratamiento de formación de trombos. En este caso, el compuesto se puede usar solo o en combinación con los agentes terapéuticos conocidos listados más adelante, preferiblemente para administración oral.

Fármacos para la prevención o tratamiento de formación de trombos: inhibidores de coagulación de la sangre [v.gr., heparina sódica, heparina de calcio, warfarina de calcio (Warfarin), etc.], fármacos trombolíticos [v.gr., urocinasa], fármacos antiplaquetas [v.gr., aspirina, sulfinpirazona (Anturan), dipiridamol (Persantin), ticlopidina (Panaldine), cilostazol (Pletal), clopidogrel etc.].

Además, el compuesto (I) tiene actividad elevadora de nivel de colesterol-lipoproteína de alta densidad superior y es de baja toxicidad. Por lo tanto, estos compuestos y sales de los mismos se pueden usar con seguridad como, por ejemplo, un agente para prevención o tratamiento de lipoproteína de baja o alta densidad primaria-colesterolemia, enfermedad de Tangier o similar, así como un agente para la prevención o tratamiento de infarto cardiaco, enfermedad aterosclerótica, hiperlipemia, anormalidad de lípidos de tipo mixto, diabetes, complicación diabética o similar y se pueden usar para prevenir o tratar arterioesclerosis, hiperlipemia, hipertensión, diabetes, complicación diabética, nefropatía diabética, neuropatía diabética, retinopatía diabética, arritmia, enfermedad vascular periférica, trombosis, trastorno pancreático, enfermedad cardiaca isquémica, isquemia cerebral, secuela de infarto cardiaco, insuficiencia cardiaca, enfermedad vascular cardiaca o enfermedad de

Alzheimer, en un mamífero (v.gr., ratón, rata, hámster, conejo, gato, perro, ganado vacuno, caballo, oveja, mono, humano y similares). Además, el compuesto (I) es adecuado para tratar y prevenir hipoHDLemia (que incluye hipoHDLemia primaria), enfermedad de Tangier, y enfermedad cardiaca isquémica, es decir, desarrollada frecuentemente en un paciente diabético después de menopausia. Además, el compuesto (I) es en particular adecuado para tratar y prevenir hiperlipemia, en particular, hipertrigliceridemia, hiperlipoproteinemia e hipercolesterolemia, así como lesión de aterosclerosis vascular que surge de la misma y las enfermedades secundarias de la misma tales como enfermedad de arteria coronaria, isquemia cerebral, aneurisma, arterioesclerosis cerebral, arterioesclerosis periférica, claudicación intermitente, gangrena y similares

Como un ejemplo notable adicional para la aplicación del compuesto (I), se ilustra la prevención o tratamiento de enfermedad de Alzheimer. Se ha sabido que el incremento de colesterol en la sangre es un factor de riesgo de enfermedad de Alzheimer. El compuesto (I) se puede usar para la prevención o tratamiento de enfermedad de Alzheimer debido a su actividad elevadora de nivel de colesterol-lipoproteína de alta densidad y actividad reductora de lípidos superiores, y cuando el compuesto (I) se usa para ese propósito, se puede administrar solo o en combinación con los

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siguientes fármacos. En este caso, la posible combinación incluye combinaciones con un inhibidor de acetilcolinesterasa (v.gr., Aricept, Excelon y similares), un inhibidor de producción o secreción de amiloide β (v.gr., un inhibidor de a y o β secretasa tal como JT-52, LY-374973 y similares, o SIB-1848 y similares), un inhibidor de coagulación de amiloide β (v.gr., PTI-00703, BETABLOC (AN-1792) y similares) y similares.

Además, puesto que el compuesto (I) tiene actividad reductora de glucosa en la sangre y muestra actividad reductora de glucosa en la sangre en una rata que padece diabetes endomórfica, mejora la resistencia a la insulina. En vista de sus características biológicas, es especialmente adecuada para la prevención o tratamiento de hiperglicemia y la enfermedad secundaria que surge de la misma tal como complicaciones observadas en la etapa diabética, nefropatía e insuficiencia renal, enfermedad circulatoria tal como anemia, anormalidad del metabolismo de los huesos, vómito, náusea, anorexia y diarrea, síntomas nerviosos tales como neuropatía, nefropatía diabética, retinopatía diabética, trastorno vascular cerebral, así como resistencia a la insulina y enfermedad que surge de la misma tal como hipertensión y tolerancia a la glucosa alterada y la enfermedad secundaria tal como enfermedad cardiaca, insuficiencia cardiaca,

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enfermedad cardiaca isquémica, isquemia cerebral, claudicación intermitente y gangrena.

En el tratamiento de estas enfermedades, el agente elevador de nivel de colesterol-lipoproteína de alta densidad de la presente invención se puede usar solo para prevención o tratamiento, o se puede usar en combinación con otros fármacos reductores de glucosa en la sangre o fármacos hipotensivos. En este caso, estos compuestos se administran preferiblemente con preparaciones orales (que incluyen tabletas de desintegración intraoral). Alternativamente, si es necesario, los compuestos se pueden administrar como preparaciones rectales en forma de supositorio. Los ingredientes que se pueden combinar en este caso incluyen (I) una preparación de insulina (v.gr., insulina humana y similares), (2) un agente de sulfonilurea (v.gr., glibenclamida, gliclazida, glimepirida y similares), (3) un inhibidor de α-glucosidasa (v.gr., voglibosa, acarbosa y similares), (4) un sensibilizador de insulina (v.gr., pioglitazona, rosiglitazona y similares), (5) un inhibidor de aldosa reductasa (v.gr., Epalrestat, Torestat y similares), y un inhibidor de glicación (v.gr., aminoguanidina y similares).

Una combinación con un fármaco para tratamiento de enfermedad ginecológica (un fármaco para tratamiento de trastorno

climatérico (estrógeno conjugado, estradiol, enahtato de testosterona, valerato de estradiol y similares), un fármaco para tratamiento de cáncer de mama (citrato de tamoxifén y similares), un fármaco para tratamiento de endometriosis e histeromioma (acetato de leuprorelin, danazol y similares) o similar, o una combinación con ese fármaco y un fármaco para tratamiento de diabetes también es posible.

Además, una combinación con un agente hipotensivo es posible, y el agente incluye, por ejemplo, (1) un diurético (v.gr., furosemida, espironolactona y similares), (2) un inhibidor de nervio simpático (v.gr., atenolol y similares), (3) un antagonista de receptor de angiotensina II (v.gr., losartan, candesartan cilexetilo, valsartan, irbesartan, olmesartan y similares), (4) un inhibidor de enzima convertidora de angiotensina I (v.gr., maleato de enalapril, clorhidrato de delapril y similares), (5) un antagonista de calcio (v.gr., nifedipina, clorhidrato de manidipina, besilato de amlodipina y similares) y similares.

Además, una combinación con un fármaco para tratamiento de insuficiencia cardiaca crónica es posible, y el fármaco incluye, por ejemplo, (1) un bloqueador de receptor β, (2) un inhibidor de ACE [v.gr., maleato de enalapril {renivace), lisinopril (longes, zestril etc.)], (3) un antagonista de receptor de angiotensina II [v.gr., candesartan, cilexetil (blopress), valsartan, losartan,

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etc.], (4) un antagonista de aldosterona (espironolactona, eplerenona), (5) un antagonista de endotelina, (6) un inhibidor de intercambio de Na-H, (7) un inhibidor de intercambio de Na-Ca, (8) un MCC-135 y similares.

El compuesto (I) tiene actividad protectora de músculo esquelético superior. Es decir, el compuesto (I) presenta efecto de tratamiento o prevención contra una condición en la cual el músculo esquelético es necrosado o sufre coalicuación, causada por varios factores tales como isquemia, esfuerzo, exceso de ejercicio, trauma (contusión, sangrado de músculo esquelético, choque eléctrico), quemadura, hipertermia maligna, síndrome maligno, miopatía metabólica, miopatía inflamatoria, distrofia muscular, infección, intoxicación, anormalidad del metabolismo e hipertermia. De manera más específica, el compuesto (I) protege al músculo esquelético contra trastorno celular que resulta de los factores anteriores. Además, el compuesto (I) tiene efecto de tratamiento o prevención contra mialgia que resulta de citotoxicidad de otros fármacos (v.gr., fármacos de HMG-CoA reductasa inhibidores, ciclosporina, fibrato, etc.) y además, rabdomiolisis en un caso severo, etc..

En particular, el compuesto (I) tiene efecto de tratamiento o prevención superior contra mialgia inducida por un inhibidor de HMG-CoA reductasa y además, rabdomiolisis severa, e inhibe la disminución de pirofosfato de

geranilgeranilo en una célula muscular inducida por un inhibidor de HMG-CoA reductasa (v.gr., atorvastatina, lovastatina, simvastatina, pravastatina, rosuvastatina, itavastatina, fluvastatina, cerivastatina, pitavastatina, etc.).

El compuesto (I) tiene actividad protectora de músculo esquelético superior y es de baja toxicidad. Por lo tanto, el agente de la presente invención se puede usar de manera segura, por ejemplo, como un agente para prevenir o tratar rabdomiolisis, mioglobinuria asociada con rabdomiolisis, o mialgia, en un mamífero (v.gr., ratón, rata, hámster, conejo, gato, perro, vaca, caballo, oveja, mono, humano, etc.).

El compuesto (I) tiene actividad incrementadora de ubiquinona superior y efecto de prevención o tratamiento contra el efecto inhibidor de progresión de disfunción de órganos e insuficiencia de órganos, y por lo tanto, es útil como un agente para prevenir o tratar y para inhibir la progresión de enfermedades con base en esta actividad farmacológica. aquí, la disfunción de órganos incluye hipofunción de varios órganos y complicaciones de los mismos y, entre otros, se prefiere disfunción de órganos isquémica. Es decir, el compuesto de la presente invención puede prevenir la muerte celular causada por isquemia o similar y puede proteger la función de una célula y un órgano, y por lo

tanto, también se puede usar como un agente para mantener la función de un órgano, un agente para proteger un órgano, un inhibidor de muerte de células de un órgano, o similar. De manera específica, el compuesto de la presente invención puede prevenir o tratar hipofunción cardiaca (que incluye daño de músculo cardiaco), hipofunción cerebral e hipofunción pancreática que resulta de varios factores (en particular, basado en isquemia) y la insuficiencia de cada órgano y puede inhibir el progreso hasta la muerte.

Además, la disfunción de órganos puede ser una disfunción de órganos que resulta de enfermedades tales como enfermedades arterioescleróticas (infarto cardiaco, angina de pecho, infarto cerebral, hemorragia cerebral, etc.) que incluye enfermedad cardiaca isquémica, o puede ser disfunción de órganos que ocurre durante o después de una operación o trasplante de un órgano. Además, el agente de la presente invención también es útil para prevenir la progresión, mejorar el pronóstico, y prevenir desarrollo secundario y recurrencia de enfermedades (en particular, enfermedad isquémica tal como enfermedad cardiaca isquémica o infarto cerebral) que son causad de las disfunciones de órganos antes mencionadas.

Aquí, el órgano incluye, por ejemplo, cerebro, hígado, riñón, cardiaco, bazo, páncreas, ojo (retina), y tejido nervioso (tejido nervioso central, tejido nervioso

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periférico, etc.); preferiblemente, tejido nervioso periférico y, entre otros, se prefiere tejido cardiaco y nervioso.

Al tener tanto actividad inhibidora de escualeno sintasa como actividad incrementadora de ubiquinona permite la aplicación del agente al pronóstico de enfermedad isquémica o similar en cerebro, corazón, riñón, tejido nervioso, páncreas o similar. Por ejemplo, en el caso de un cerebro (tejido nervioso), que inhibe el progreso a un coma, el mantenimiento de la conciencia o la prolongación la vida se hace posible, y enfermedad de Parkinson o enfermedad de Alzheimer que resulta de enfermedad neurodegenerativa central se puede tratar. Además, se hace posible el tratamiento del entumecimiento de las manos y los pies, impercepción, dolor, anormalidad de sensibilidad térmica, úlcera, o hiporeflexia nerviosa que resulta de neuropatía periférica. En el caso de un corazón, se hace posible el tratamiento de insuficiencia cardiaca o arritmia, o la prolongación de la vida. En el caso de riñones, se hace posible la inhibición del progreso a diálisis o trasplante renal, o prolongación de la vida.

El compuesto de la presente invención tiene actividad incrementadora de ubiquinona superior y efecto de prevención o tratamiento contra disfunción de órganos o insuficiencia de órganos, y es de baja toxicidad. Por lo tanto, el compuesto de la presente invención se puede usar

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con seguridad como un agente para prevenir o tratar infarto de miocardio, enfermedad arterioesclerótica, hiperlipemia, infarto cerebral, hemorragia cerebral, enfermedad neurodegenerativa o diabetes, o complicaciones diabéticas, además de un agente de prevención o tratamiento y un agente para inhibir la progresión de disfunción de órganos o insuficiencia de órganos.

El compuesto (I) se puede usar para tratar o prevenir arterioesclerosis, hiperlipemia, anormalidad de lípidos de tipo mixto, diabetes, complicaciones diabéticas, nefropatía diabética, neuropatía diabética, retinopatía diabética, arritmia, enfermedad vascular periférica, trombosis, trastorno pancreático, enfermedad cardiaca isquémica, CHD (enfermedad cardiaca coronaria), isquemia cerebral, infarto cardiaco, la secuela de infarto cardiaco, enfermedad vascular cardiaca o enfermedad de Alzheimer. Además, el compuesto (I) se puede usar para prevenir o tratar infarto cardiaco; hemorragia cerebral; poloaciuria, incontinencia urinaria o excreción deteriorada de la vejiga urinaria basada en neuropatía; enfermedad de Parkinson basada en enfermedad neurodegenerativa; y demencia vascular cerebral, además de insuficiencia cardiaca e insuficiencia renal. El compuesto (I) también es útil para inhibir muerte causada por estas enfermedades o prolongación de la vida.

Además, se ha reportado que la ubiquinona activa la

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función de la UCP (proteína no acopladora). Por lo tanto, el compuesto (I) es útil para prevenir o tratar obesidad y es adecuado para prevenir o tratar tolerancia a la glucosa alterada, diabetes, resistencia a la insulina, hipertensión, hiperlipemia o similar asociada con obesidad.

Puesto que el compuesto (I) tiene tanto actividad inhibidora de escualeno sintasa como actividad incrementadora de ubiquinona además de actividad mejoradora de metabolismo de lípidos tal como actividad reductora de colesterol, actividad reductora de triglicéridos y actividad elevadora del nivel de colesterol-lipoproteína de alta densidad (HDL), se puede usar de manera extremadamente ventajosa para prevenir o tratar disfunción de órganos o insuficiencia de órganos, entre otros, disfunción de órganos o insuficiencia de órganos que resulta de enfermedades tales como enfermedad arterioesclerótica (infarto cardiaco, angina de pecho, infarto cerebral, hemorragia cerebral, etc.) que incluye enfermedad cardiaca isquémica. Además, puesto que el compuesto (I) tiene actividad incrementadora de ubiquinona además de actividad reductora de lípidos, por ejemplo, puede tratar enfermedad cardiaca isquémica, prevenir o tratar insuficiencia cardiaca más severa, e inhibir el progreso de insuficiencia cardiaca hasta la muerte, y por lo tanto es extremadamente útil en comparación con un agente reductor de lípidos que no tiene actividad incrementadora de ubiquinona.

Además, en relación con otros órganos tales como cerebro, riñón y tejido nervioso, el compuesto (I) que tiene actividad incrementadora de ubiquinona además de actividad reductora de lípidos es excelente en términos de ser capaz de prevenir o tratar insuficiencia de órganos o tejidos además de disfunción de órganos, y también tiene efecto de prolongación de la vida.

Cuando el compuesto (I) se aplica a las diversas enfermedades antes mencionadas, se puede usar en combinación con sustancias biológicas (v.gr., anticuerpos, preparaciones de vacuna, etc.). Alternativamente, el compuesto (I) se puede aplicar como una terapia de combinación en combinación con terapia génica. Los anticuerpos y preparaciones de vacuna incluyen preparaciones de vacuna dirigidas a angiotensina II, preparaciones de vacuna dirigidas a CETP, anticuerpos de CETP, anticuerpos de FNT α y anticuerpos dirigidos a otra citocina, preparaciones de vacuna de amiloide β, y vacunas de diabetes de tipo 1 (DIAPEP-277 de Peptor Company, etc.), así como anticuerpos o preparaciones de vacuna dirigidas a citocina, enzimas de renina-angiotensina y los productos de las mismas, anticuerpos o preparaciones de vacuna dirigidas a enzimas o proteínas implicadas en metabolismo de lípidos de la sangre, anticuerpos o vacunas relacionadas con enzimas o proteínas implicadas en sistema de coagulación o

fibrinogenólisis en la sangre, y anticuerpos o preparaciones de vacuna dirigidas a proteínas implicadas en el metabolismo de la glucosa o resistencia a la insulina. La terapia génica incluye terapias que usan genes asociados con citocina, enzimas de renina-angiotensina y los productos de las mismas, terapias que usan señuelo de ADN tal como señuelo de NFKB, terapias que usan antisentido, terapias que usan genes asociados con enzimas o proteínas implicadas en el metabolismo de lípidos en la sangre (v.gr., genes asociados con metabolismo, excreción o absorción de colesterol, triglicérido, Colesterol-HDL o fosfolípidos de la sangre), terapias que usan genes asociados con enzimas o proteínas (v.gr., factores de crecimiento tales como HGF, VEGF, etc.) implicadas en terapia de vascularización para obstrucción vascular periférica, terapias que usan genes asociados con proteínas implicadas en el metabolismo de la glucosa o resistencia a la insulina, y antisentido para citocina tal como FNT. Alternativamente, el compuesto (I) se puede usar en combinación con varios métodos de regeneración de órganos tales como regeneración de corazón, regeneración de riñón, regeneración o revascularización de páncreas, o terapia de vascularización que utiliza trasplante de células de médula ósea (célula mononuclear de médula ósea, células madre de médula ósea, etc.).

Cuando el compuesto (I) se combina con otros

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fármacos bajo aplicación con las enfermedades respectivas antes mencionadas, estos ingredientes activos se pueden administrar como un agente combinado obtenido al formularlos en una preparación.

El compuesto (I) se puede usar oralmente o parenteralmente por inyección, infusión, inhalación, administración rectal o administración local, y se puede usar como tal o como una composición farmacéutica (v.gr., polvos, gránulos, tabletas, píldoras, cápsulas, inyecciones, jarabes, emulsiones, elíxires, suspensiones, soluciones, etc.). Es decir, por lo menos un compuesto (I) se puede usar solo o como una mezcla de un vehículo farmacéuticamente aceptable (adyuvante, excipiente, aditivo y/o diluyente).

Para la medicina de la presente invención, el compuesto (I) que es el ingrediente activo se puede administrar como polvo a granel, pero generalmente, se administra en una forma preparada por un método convencional con el uso apropiadamente de una cantidad apropiada de un vehículo farmacéutico convencional, por ejemplo, un excipiente (v.gr., carbonato de calcio, caolina, bicarbonato de sodio, lactosa, almidón, celulosa cristalina, talco, azúcar granulado, sustancias porosas, etc.), un aglutinante (v.gr., dextrina, gomas, almidón alcoholados, gelatina, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, pululano, etc.), un desintegrante (v.gr., carboximetilcelulosa

potásica, croscarmelosa sódica, crospovidona, hidroxipropilcelulosa baja-sustituida, parcialmente α-almidón, etc.), un lubricante (v.gr., estearato de magnesio, estearato de calcio, talco, almidón, benzoato de sodio, etc.}, un agente colorante (v.gr., colorante de alquitrán, caramel, sesquióxido de hierro, dióxido de titanio, riboflavinas), un corrector (v.gr., edulcorante, sabor, etc.), un estabilizador (v.gr., sulfito de sodio, etc.) y un conservador (v.gr., parabenos, ácido sórbico, etc.). La medicina de la invención que incluye el agente antes mencionado generalmente contiene el compuesto (I) en una cantidad efectiva para el tratamiento y prevención de enfermedad. El contenido del compuesto de la fórmula (I) en la medicina de la presente invención es generalmente 0.1 a 100% en peso de la preparación total. La medicina usada en la presente invención puede contener ingredientes de fármaco distintos al compuesto (I) como un ingrediente activo, los ingredientes no están limitados en particular siempre que se logre el objeto de la invención, y se pueden usar en una relación de combinación apropiada. Ejemplos específicos de la forma de dosis incluyen tabletas (que incluyen tabletas revestidas de azúcar, tabletas revestidas de película), píldoras, cápsulas, gránulos, gránulos finos, polvos, jarabes, emulsiones, suspensiones, inyecciones, inyecciones

de liberación sostenida, inhalantes, y ungüentos. Esas preparaciones se preparan de conformidad con un método convencional (v.gr., un método descrito en Japanese Pharmacopoeia).

De manera específica, una tableta se puede producir al granular el compuesto (I) solo o una mezcla uniforme del compuesto (I) y un excipiente, un aglutinante, un desintegrante u otro aditivo adecuado por un método adecuado, seguido por la adición de un lubricante o similar, y después al comprimir el gránulo resultante; al comprimir directamente el compuesto (I) solo o una mezcla uniforme del compuesto (I) y un excipiente, un aglutinante, un desintegrante u otro aditivo adecuado; o al comprimir un gránulo preparado con anticipación solo o una mezcla uniforme del gránulo y un aditivo adecuado. La presente tableta puede contener un agente colorante, un corrector o similar si es necesario. La presente tableta también se puede revestir con un agente de revestimiento adecuado. Una inyección se puede preparar al disolver, suspender o emulsionar una cierta cantidad del compuesto (I) en agua para inyección, solución salina fisiológica, solución de Ringer o similar para un solvente acuoso, o en un aceite vegetal convencional o similar para un solvente no acuoso para obtener una cierta cantidad de la inyección resultante, o al poner una cierta cantidad del compuesto (I) en un contenedor para inyección y después

sellarlo.

Un vehículo para una preparación oral incluye substancias usadas convencionalmente en la técnica de preparación de fármacos tales como almidón, manitol, celulosa cristalına, carboximetilcelulosa sódica, etc.. Un vehículo para inyección incluye agua destilada, una solución salina fisiológica, una solución de glucosa y una solución de infusión. Además, otros aditivos usados para preparación general se puede añadir de manera adecuada.

La medicina de la presente invención también se puede usar como una preparación de liberación sostenida. La preparación de liberación sostenida puede ser una microcápsula (v.gr., microcápsula de microesfera, micropartícula, etc.) ya que se prepara por un método de secado-en-agua (o/c método, c/o/c método, etc.), un método de separación de fases, secado por aspersión o una manera similar al mismo, o una preparación obtenida al formular la microcápsula o una composición farmacéutica en forma de esfera, forma de aguja, forma de comprimido, forma de película o forma de crema, como material de partida, en varias formas de dosis. La forma de dosis incluye una preparación parenteral (v.gr., una inyección o un implante intramuscular, subcutánea, órgano, etc.; un agente intramucosa para cavidad nasal, recto, útero, etc.), y una preparación oral (v.gr., cápsula dura, cápsula blanda,

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gránulo, polvo, suspensión, etc.).

Cuando la preparación de liberación sostenida es una inyección, la preparación de liberación sostenida se prepara al suministrar la microcápsula en un agente de dispersión (v.gr., agentes tensoactivos tales como Tween 80, HCO-60, etc.; polisacáridos tales como carboximetilcelulosa, arginato de sodio, hialuronato de sodio, etc.; sulfato de protamina, polietileneglicol, etc.), conservadores (v.gr., metilparabeno, propilparabeno, etc.), agentes isotonizantes (v.gr., cloruro de sodio, manitol, sorbitol, glucosa, etc.), anestésicos locales (v.gr., clorhidrato de xilocaína, clorobutanol, etc.), etc. para dar una suspensión acuosa, o al dispersar la microcápsula en aceite vegetal (v.gr., aceite de ajonjolí, aceite de maíz, etc.) o una mezcla del mismo con fosfolípidos (v.gr., lecitina, etc.) o triglicéridos de ácido graso de cadena media (v.gr., Miglyol 812, etc.) para dar una solución oleosa.

Cuando la preparación de liberación sostenida es una microcápsula, su diámetro de partícula promedio es de aproximadamente 0.1 a aproximadamente 300 μm, preferiblemente de aproximadamente 1 a aproximadamente 150 μm, preferiblemente aún de aproximadamente 2 a aproximadamente 100 μm.

Cuando la microcápsula se formula en una

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preparación estéril, hay un método que comprende esterilizar los pasos completos de preparación, un método que comprende esterilizar con el uso de rayos gamma, un método que comprende añadir un antiséptico, etc , pero el método no es específicamente limitado La medicina de la presente invención se puede formular en una preparación de conformidad con un método convencional Esa preparación se puede preparar generalmente al mezclar/amasar un ingrediente activo con un aditivo tal como un excipiente, un diluyente o un vehículo "Parenteral", cuando se usa aquí, incluye inyección subcutánea, inyección intravenosa, inyección intramuscular, inyección intraperitoneal e infusión Una preparación inyectable, por ejemplo, una suspensión acuosa u oleosa estéril para inyección se puede preparar con el uso de un agente dispersante o agente humectante adecuado y un agente de suspensión adecuado por un método conocido en la técnica La preparación inyectable estéril puede ser una solución o suspensión inyectable estéril en un diluyente o un solvente, que es no tóxico y se puede administrar parenteralmente, por ejemplo, una solución acuosa Un vehículo o solvente aceptable que se puede usar incluye agua, solución de Ringer, y una solución isotónica de cloruro de sodio Un aceite no volátil estéril también se puede usar generalmente como un solvente o un solvente de suspensión Para esto, se puede usar cualquier aceite volátil o ácido graso, que incluye

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aceite graso o ácido graso sintético o semisintético, y mono-, di- o triglicéridos naturales o sintéticos.

Un supositorio para administración rectal se puede preparar al mezclar el fármaco con un aditivo no estimulante apropiado, por ejemplo, un aditivo que es sólido a la temperatura normal pero es líquido a la temperatura de un tracto intestinal, se derrite en el recto y libera un fármaco, tal como manteca de cacao o polietilenglicol.

Ejemplos de una forma de dosis sólida para administración oral incluyen los polvos, gránulos, tabletas, píldoras y cápsulas, etc., antes mencionados. Una preparación en esa forma de dosis se puede preparar al mezclar y/o amasar un compuesto de ingrediente activo con por lo menos un aditivo, por ejemplo, sacarosa, lactosa, azúcar de celulosa, manitol (D-manitol), maltitol, dextrano, almidones (v.gr., almidón de maíz), celulosa microcristalina, agar, alginatos, quitinas, quitosanes, pectinas, gomas tragacanto, gomas arábigas, gelatinas, colágenos, caseínas, albúmina, y polímeros o glicéridos sintéticos o semisintéticos. Esas formas de dosis pueden contener aditivos adicionales como es usual, y esos aditivos incluyen un diluyente inerte, un lubricante tal como ácido esteárico y estearato de magnesio, un conservador tal como parabenos y ácido sórbico, un antioxidante tal como ácido ascórbico, α-tocoferol y

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cisteína, un desintegrante (v.gr., croscarmelose sódica), un aglutinante (v.gr., hidroxipropilcelulosa), un espesante, un regulador de pH, un edulcorante, un sabor, y un perfume. Las tabletas y píldoras se pueden preparar por revestimiento entérico adicional. Las soluciones para administración oral incluyen emulsiones, jarabes, elíxires, suspensiones y soluciones farmacéuticamente aceptables. Pueden contener un diluyente inerte que se usa convencionalmente en la técnica, por ejemplo, agua y, si es necesario, aditivos. Estas soluciones orales se pueden preparar de conformidad con un método convencional, por ejemplo, al mezclar un compuesto de ingrediente activo y un diluyente inerte y, si es necesario, otros aditivos.

Una preparación oral puede contener, según la forma de dosis, por lo general de aproximadamente 0.01 a 99% en peso, preferiblemente de aproximadamente 0.1 a 90% en peso, por lo general de aproximadamente 0.5 a 50% del compuesto de ingrediente activo de la presente invención.

La dosis para un paciente particular se determina según la edad, peso, condición de salud general, sexo, dieta, tiempo de administración, método de administración, velocidad de secreción, combinación de fármacos, y grado de síntoma del paciente que ha de ser tratado, o al considerar estos y otros factores.

El compuesto de la presente invención tiene

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actividad inhibidora de escualeno sintasa, actividad reductora de colesterol y actividad reductora de triglicéridos, y tiene alta selectividad para transición a un órgano objetivo y un amplio margen de seguridad. Por lo tanto, el compuesto de la presente invención es útil para prevenir o tratar hiperlipemia como un agente reductor de lípidos y también es útil para prevenir o tratar arterioesclerosis.

Una medicina que contiene el compuesto (I) de la presente invención es de baja toxicidad y se puede usar de manera segura. La dosis diaria de la medicina varía según la condición y peso de un paciente, el tipo de un compuesto y la vía de administración, etc. Por ejemplo, cuando la medicina se usa como un agente para prevenir o tratar hiperlipemia, la dosis diaria para un adulto (peso corporal de aproximadamente 60 kg) es de aproximadamente 1 a 500 mg, preferiblemente de aproximadamente 10 a 200 mg del ingrediente activo [el compuesto (I)] en el caso de una preparación oral, y es de aproximadamente 0.1 a 100 mg, preferiblemente de aproximadamente 1 a 50 mg, por lo general de aproximadamente 1 a 20 mg del ingrediente activo 5 en el caso de una preparación parenteral. No se encuentra toxicidad dentro del intervalo.

Los siguientes ejemplos, ejemplos de preparación y ejemplos experimentales explicarán la presente invención en

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detalle, pero la presente invención no se limita a los mismos.

El espectro de ^{1}H-RMN se midió por espectómetro de tipo Varian Gemini 200(200 MHz) o de tipo 300(300 MHz) con el uso de tetrametilsilano como un estándar interno. Todos los valores se muestran en ppm. El valor numérico denotado para un solvente mixto es la relación mixta de solventes respectivos con base en volumen a menos que se indique otra cosa. % significa % en peso a menos que se indique otra cosa. La relación de solventes de elución para cromatografía sobre gel de sílice se basa en volumen a menos que se indique otra cosa. La temperatura ambiente (temperatura normal), como se usa aquí, es de aproximadamente 20°C a aproximadamente 30°C.

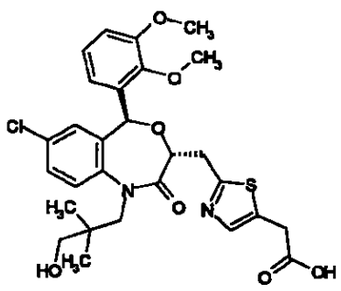
Los símbolos respectivos en los ejemplos tienen los siguientes significados:

Ac: acetilo, Pr: n-propilo, Me: metilo, Bu: n-butilo, Et: etilo, ^{i}Pr: isopropilo, Et_2O: éter dietílico, DMF: N,N-dimetilformamida, DMSO: sulfóxido de dimetilo, THF: tetrahidrofurano, s: singulete, d: doblete, t: triplete, q: cuadriplete, dd: doble doblete, dt: doble triplete, m: multiplete, br: ancha, J: constante de acoplamiento

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EJEMPLO 1

Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acético



(1) Se añadió carbonilodiimidazol (10.2 g, 63.1 mmoles) a una suspensión de ácido 2-(ter-butoxicarboniloamino)acético (10 g, 57.1 mmoles) en THF (100 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. A la solución de reacción se añadieron cloruro de magnesio (5.4 g, 57.1 mmoles) y monoetilmalonato de potasio (9.7 g, 57.1 mmoles) y la mezcla se agitó a 60°C durante 1 hora. La mezcla se filtró para remover sustancias insolubles. El filtrado se diluyó con acetato de etilo (200 ml), se lavó con ácido clorhídrico 1 N, una solución acuosa de bicarbonato de sodio y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (2:1)] para obtener 4-(ter-butoxicarboniloamino)-3-oxobutanoato de etilo (11.9 g, 48.5 mmoles, 85%)como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 1.29 (3H, t, J = 7.4 Hz), 1.45 (2H, s), 3.87 {2H, s), 3.96 (3H, s), 4.21 (2H, q, J = 7.2 Hz), 7.08 (1H, d, J = 8.7 Hz), 7.39 (9H, s), 3.49 (2H, s), 4.14 (2H, d, J = 5.8 Hz), 4.21 (2H, q, J = 7.4 Hz), 5.15-5.24 (1H, br).

(2) Se añadió solución 4 N de HCl en acetato de etilo (50 ml) a una solución de 4-(ter-butoxicarboniloamino)-3-oxobutanoato de etilo (11 g, 44.8 mmoles) obtenido en el ejemplo 1-(1) en ácido acético (6 ml) y la mezcla se agitó a temperatura ambiente durante 30 minutos. La solución de reacción se concentró bajo presión reducida y el residuo se cristalizó a partir de acetato de etilo para obtener clorhidrato de 4-amino-3-oxobutanoato de etilo (7.9 g, 43.5 mmoles, 97%) como polvo incoloro.

^{1}H-RMN (CD_3OD) δ: 1.27 (3H, t, J = 7.2 Hz), 3.69 (2H, 25 s), 4.124 (2H, s), 4.20 (2H, q, J = 7.2 Hz).

(3) Se añadió cloruro de pivaloilo (0.51 g, 4.23 mmoles) a una solución de ácido 2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acético (2 g, 3.85 mmoles) y trietilamina (0.41 g, 4.04 mmoles) en acetonitrilo (15 ml) a 0°C y la mezcla se agitó a 0°C durante 30 minutos. A la solución de reacción se añadió clorhidrato de 4-amino-3-oxobutanoato de etilo (0.84 g, 4.62 mmoles) obtenido en los

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ejemplos 1-(2) a 0°C y después se añadió gota a gota una solución de trietilamina (0.58 g, 5.77 mmoles) en acetonitrilo (2 ml).

Después de agitarse a temperatura ambiente durante 30 minutos, la solución de reacción se diluyó con acetato de etilo (50 ml), se lavó con ácido clorhídrico 0.1 N, una solución acuosa al 5% de sulfato ácido de potasio, una solución acuosa de bicarbonato de sodio y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (1:3)] para obtener 4-({2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]acetil}amino)-3-oxobutanoato de etilo (1.8 g, 2.75 mmol, 71%) como polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.01 (3H, s), 1.28 (3H, t, J = 7.0 Hz), 2.03 (3H, s), 2.71 (1H, dd, J = 5.6, 14.8 Hz), 2.79 (1H, dd, J = 7.4, 14.8 Hz), 3.48 (2H, s), 3.54 (1H, d, J = 14.2 Hz), 3.62 (3H, s), 3.71 (1H, d, J = 11.4 Hz), 3.86 (1H, d, J = 11.4 Hz), 3.89 (3H, s), 4.14-4.25 (4H, m), 4.37 (1H, dd, J = 5.6, 7.4 Hz), 4.55 (1H, d, J = 14.2 Hz), 6.26 (1H, s), 6.58-6.62 (1H, br), 6.63 (1H, s), 6.96-7.33 (5H, m).

(4) Una solución de 4-({2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]acetil}amino)-3-oxobutanoato de etilo (0.5 g, 0.773 mmoles) obtenido en el ejemplo 1-(3) y un reactivo de Lawesson (0.46 g, 1.16 mmoles) en THF (5 ml) se agitó a 70°C durante 1 hora. La solución de reacción se concentró bajo presión reducida y el residuo se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (1:1)] para obtener (2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acetato de etilo (0.41 g, 0.635 mmoles, 82%) como polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.03 (3H, s), 1.28 (3H, t, J = 7.2 Hz), 2.03 (3H, s), 3.44 (1H, dd, J = 7.2, 15.0 Hz), 3.55 (1H, dd, J = 6.9, 15.0 Hz), 3.58 (1H, d, J = 14.4 Hz), 3.62 (3H, s), 3.73 (1H, d, J = 10.8 Hz), 3.80 (2H, s), 3.85 (1H, d, J = 10.8 Hz), 3.89 (3H, s), 4.20 (2H, q, J = 7.2 Hz), 4.33 (1H, dd, J = 6.9, 7.2 Hz), 4.57 (1H, d, J = 14.4 Hz), 6.31 (1H, s), 6.60 (1H, t, J = 2.1 Hz), 6.96-7.34 (5H, m), 7.43 (1H, s).

(5) Una mezcla de (2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-

il)acetato de etilo (0.3 g, 0.465 mmoles) obtenido en el ejemplo 1-(4), una solución acuosa 1 N de hidróxido de sodio (1 ml) y etanol (3 ml) se agitó a 60°C durante 30 minutos. Esta mezcla se diluyó con agua (50 ml), se acidificó y después se extrajo dos veces con acetato de etilo (50 ml). Estos extractos se lavaron con una solución acuosa saturada de cloruro de sodio, se secaron sobre sulfato de sodio, y después se concentraron bajo presión reducida. El residuo se recristalizó a partir de etanol-hexano (1:5) para obtener ácido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acético (0.23 g, 0.400 mmoles, 86%) como un cristal prismático incoloro.

p.f.: 219-222°C (dec.) (EtOH-hexano).

$[\alpha]D^{22}$-209.2° (c = 0.34, MeOH).

IR ν_{max} (KBr) cm^{-1}: 3500-2400, 1724, 1658.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 3.19 (1H, d, J = 12.3 Hz), 3.38 (1H, d, J = 14.4 Hz), 3.46 (1H, dd, J = 7.2, 15.0 Hz), 3.59 (1H, dd, J = 6.0, 15.0 Hz), 3.61 (3H, s), 3.64 (1H, d, J = 12.3 Hz), 3.82 (2H, s), 3.88 (3H, s), 4.35 (1H, dd, J = 6.0, 7.2 Hz), 4.47 (1H, d, J = 14.4 Hz), 6.20 (1H, s), 6.58 (1H, d, J = 1.8 Hz), 6.96-7.36 (5H, m), 7.48 (1H, s).

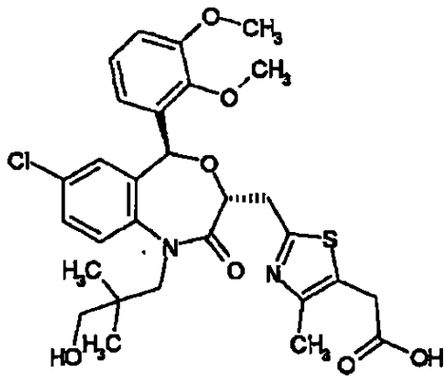
Análisis calculado para $C_{28}H_{31}N_2O_7lS$: C, 58.48; H,

5.43; N, 4.87.

Encontrado: C, 58.32; H, 5.30; N, 4.68.

EJEMPLO 2

Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-4-metil-1,3-tiazol-5-il)acético

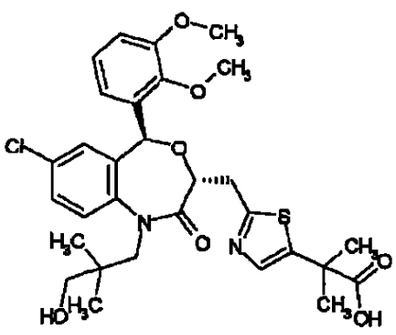


De conformidad con una manera similar a la del ejemplo 1, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.641 (3H, s), 1.05 (3H, s), 2.29 (3H, s), 3.18 (1H, d, J = 12.3 Hz), 3.37 (1H, d, J = 13.8 Hz), 3.42 (1H, dd, J = 6.9, 15.0 Hz), 3.54 (1H, dd, J = 5.4, 15.0 Hz), 3.61 (3H, s), 3.64 (1H, d, J = 12.3 Hz), 3.73 (2H, s), 3.88 (3H, s), 4.29 (1H, dd, J = 5.4, 6.9 Hz), 4.47 (1H, d, J = 13.8 Hz), 6.19 (1H, s), 6.57 (1H, d, J = 2.1 Hz), 6.96-7.35 (5H, m) .

EJEMPLO 3

Acido 2-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-2-metilpropiónico

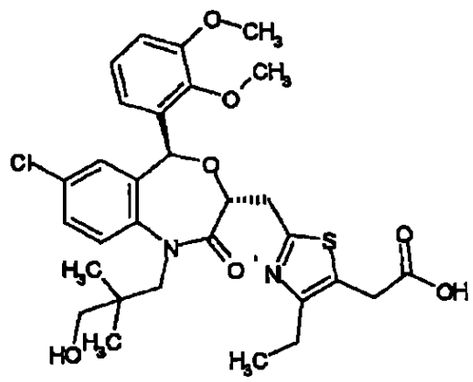


De conformidad con una manera similar a la del ejemplo 1, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.67 (3H, s), 1.04 (3H, s), 1.65 (6H, s), 3.15 (1H, d, J = 11.6 Hz), 3.41 (1H, dd, J = 7.2, 14.8 Hz), 3.41 (1H, dd, J = 14.4 Hz), 3.54 (1H, dd, J = 6.2, 14.8 Hz), 3.61 (3H, s), 3.62 (1H, d, J = 11.6 Hz), 3.89 (3H, s), 4.34 (1H, dd, J = 6.2, 7.2Hz), 4.48 (1H, d, J = 14.4 Hz), 6.20 (1H, s), 6.55 (1H, s), 6.96-7.36 (5H, m), 7.46

EJEMPLO 4

Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-4-etil-1,3-tiazol-5-il)acético

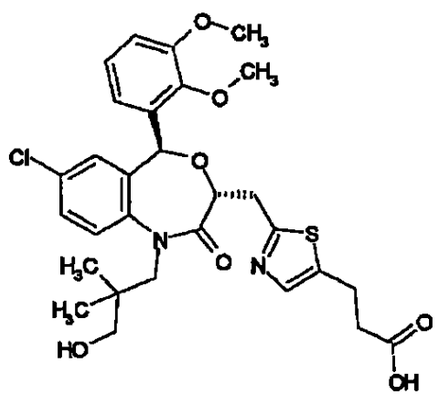


De conformidad con una manera similar a la del ejemplo 1, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 1.18 (3H, t, J = 7.5 Hz), 2.63 (2H, q, J = 7.5 Hz), 3.18 (1H, d, J = 12.0 Hz), 3.37 (1H, d, J = 14.4 Hz), 3.43 (1H, dd, J = 7.2, 15.0Hz), 3.54 (1H, dd, J = 6.0, 15.0 Hz), 3.61 (3H, s), 3.64 (1H, d, J = 12.0 Hz), 3.74 (2H, s), 3.88 (3H, s), 4.31 (1H, dd, J = 6.0, 7.2 Hz), 4.47 (1H, d, J = 14.4 Hz), 6.19 (1H, s), 6.57 (1H, d, J = 1.8Hz), 6.95-7.36 (5H, m).

EJEMPLO 5

Acido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)propiónico



(1) Carbonilodiimidazol (9.7 g, 60 mmoles) se añadió a una solución de ácido monoetilsuccínico (7.3 g, 50 mmoles) en THF (70 ml) y la mezcla se agitó a temperatura ambiente durante 1 hora. A la solución de reacción se añadió cloruro de magnesio (4.8 g, 50 mmoles) y monoetilmalonato de potasio (8.5 g, 50 mmoles) y la mezcla se agitó a 60°C durante 1 hora. La mezcla se filtró para remover sustancias insolubles y el filtrate se concentró bajo presión reducida. El residuo se diluyó con agua, se acidificó y después se extrajo dos veces con acetato de etilo (70 ml). Los extractos se lavaron con una solución acuosa saturada de cloruro de sodio, se secaron sobre sulfato de sodio, y después se concentraron bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice [solvente de

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revelado: hexano-acetato de etilo (3:1)] para obtener 3-oxohexanodioato de dietilo (8.9 g, 41.2 mmoles, 82%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 1.26 (3H, t, J = 7.2 Hz), 1.29 (3H, t, J = 7.2 Hz), 2.61 (2H, t, J = 6.6 Hz), 2.87 (2H, t, J = 6.6 Hz), 3.50 (97/100 x 2H, s), 4.14 (2H, q, J = 7.2 Hz), 4.21 (2H, q, J = 7.2 Hz), 5.02 (3/100 x IH, s) .

(2) Una solución de nitrito de sodio (3.3 g, 48 mmoles) en agua (40 ml) se añadió gota a gota a una solución de 3-oxohexanodioato de dietilo (8.7 g, 40.2 mmoles) obtenido en el ejemplo 5-(1) en ácido acético (20 ml) bajo enfriamiento con hielo. Posteriormente, se añadió agua (60 ml) y la mezcla se agitó durante la noche. La solución de reacción se extrajo dos veces con acetato de etilo (50 ml). Los extractos se lavaron con una solución acuosa de bicarbonato de sodio y una solución acuosa saturada de cloruro de sodio, se secaron sobre sulfato de sodio, y después se concentraron bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice [solución de revelado: hexano-acetato de etilo (2:1)] para obtener 2-hidroxiimino-3-oxohexanodioato de dietilo (9.3 g, 37.9 mmoles, 94%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 1.27 (3H, t, J = 7.4 Hz), 1.35 (3H, t, J = 7.4 Hz), 2.68 (2H, t, J = 6.6 Hz), 3.17 (2H, t, J

= 6.6 Hz), 4.17 (2H, q, J = 7.4 Hz), 4.38 (2H, q, J = 7.4 Hz).

(3) Se añadió polvo de zinc (18.7 g, 0.286 mol) a una solución de 2-hidroxiimino-3-oxohexanodioato de dietilo (9 g, 36.7 mmoles) obtenido en el ejemplo 5-(2) y acético anhídrido (26 g, 0.220 mol) en ácido acético (120 ml) a temperatura ambiente y la mezcla se agitó durante 24 horas. La mezcla se filtró para remover sustancias insolubles y las sustancias insolubles se lavaron con acetato de etilo (50 ml). El filtrado y la solución de lavado se combinaron y después se concentraron bajo presión reducida para obtener 2-acetilamino-3-oxohexanodioato de dietilo (9.0 g, 32.9 mmoles, 90%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 1.25 (3H, t, J = 7.2 Hz), 1.33 (3H, t, J = 7.2 Hz), 2.08 (3H, s), 2.62-2.67 (2H, m), 2.95 (1H, dt, J = 18.6, 6.6 Hz), 3.11 (1H, dt, J = 18.6, 6.6 Hz), 4.12 (2H, q, J = 7.2 Hz), 4.29 (2H, q, J = 7.2 Hz), 5.30 (1H, d, J = 6.6 Hz), 6.68 (1H, d, J = 6.6 Hz).

(4) 2-Acetilamino-3-oxohexanodioato de dietilo (8.8 g, 32.2 mmoles) obtenido en el ejemplo 5-(3) se añadió a una solución 4N de HCl en acetato de etilo (90 ml) y la mezcla se calentó a reflujo durante 4 horas. La solución de reacción se concentró bajo presión reducida y el residuo se cristalizó a partir de acetato de etilo-éter para obtener clorhidrato de

ácido 5-amino-4-oxopentanoico (4.4 g, 26.3 mmoles, 82%) como un cristal de aguja incoloro.

^{1}H-RMN (CD_3OD) δ: 2.65 (2H, t, J = 7.0 Hz), 2.81 (2H, t, J = 7.0 Hz), 4.02 (2H, s).

(5) Se añadió cloruro de pivaloilo (0.51 g, 4.23 mmoles) a una solución de ácido 2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il] acético (2 g, 3.85 mmoles) y trietilamina (0.41 g, 4.04 mmoles) en acetonitrilo (15 ml) a 0°C y la mezcla se agitó a 0°C durante 30 minutos. A la solución de reacción a 0°C, se añadió clorhidrato de ácido 5-amino-4-oxopentanoico (0.77 g, 4.62 mmoles) obtenido en el ejemplo 5-(4) y después se añadió gota a gota una solución de trietilamina (0.58 g, 5.77 mmoles) en acetonitrilo (2 ml).

Después de agitarse a temperatura ambiente durante 30 minutos, la solución de reacción se diluyó con acetato de etilo (50 ml), se lavó con ácido clorhídrico 0.1 N y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio, y después se concentró bajo presión reducida. El residuo se disolvió en DMF (30 ml), se añadieron carbonato de potasio (0.65 g, 4.69 mmoles) y yoduro de metilo (0.67 g, 4.69 mmoles), y la mezcla se agitó a temperatura ambiente durante 1 hora. La solución de reacción se diluyó con acetato de etilo (100 ml), se lavó con agua, una solución

acuosa al 5% de sulfato ácido de potasio, una solución acuosa de bicarbonato de sodio y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (1:3)] para obtener 5-({2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]acetil}amino)-4-oxopentanoato de metilo (1.2 g, 1.85 mmoles, 44%) como polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.02 (3H, s), 2.03 (3H, s), 2.60-2.76 (5H, m), 2.93 (1H, dd, J = 7.0,14.6 Hz), 3.53 (1H, d, J = 14.4 Hz), 3.61 (3H, s), 3.68 (3H, s), 3.71 (1H, d, J = 12.0 Hz), 3.86 (1H, d, J = 12.0 Hz), 3.89 (3H, s), 4.17 (2H, d, J = 4.6 Hz), 4.38 (1H, dd, J = 6.8, 7.0 Hz), 4.55 (1H, d, J = 14.4 Hz), 6.26 (1H, s), 6.58 (1H, t, J = 4.6 Hz), 6.63 (1H, s), 6.96-7.32 (5H, m).

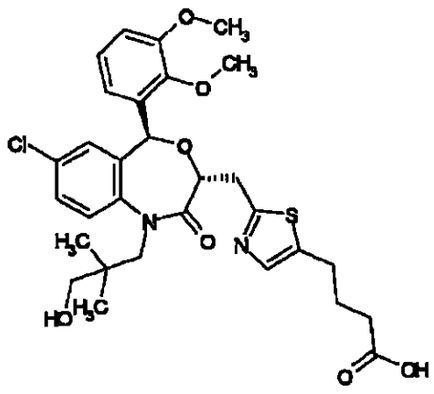
(6) De conformidad con las maneras similares a las de los ejemplos 1-(4) a (5), se obtuvo ácido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxı-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)propiónico.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.68 (2H, t, J = 7.0 Hz), 3.11 (2H, t, J = 7.0 Hz), 3.17 (1H, d, J

= 11.8 Hz), 3.38 (1H, d, J = 14.2 Hz), 3.42 (1H, dd, J = 7.0, 15.4 Hz), 3.57 (1H, dd, J = 5.8, 15.4 Hz), 3.62 (3H, s), 3.64 (1H, d, J= 11.8 Hz), 3.89 (3H, s), 4.34 (1H, dd, J= 5.8, 7.0 Hz), 4.48 (1H, d, J = 14.2 Hz), 6.20 (1H, s), 6.58 (1H, s), 6.97-7.37 (6H, m).

EJEMPLO 6

Acido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)butanoico



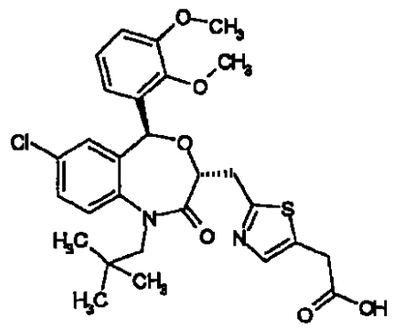
De conformidad con una manera similar a la del ejemplo 5, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 1.96 (2H, quintuplete, J = 7.0 Hz), 2.41 (2H, t, J = 7.0 Hz), 2.86 (2H, t, J = 7.0 Hz), 3.17 (1H, d, J = 11.8 Hz), 3.38 (1H, d, J = 14.4 Hz), 3.43 (1H, dd, J = 7.0, 15.0 Hz), 3.57 (1H, dd, J = 5.8, 15.0 Hz), 3.62 (3H, s), 3.64 (1H, d, J = 11.8 Hz),

3.89 (3H, s), 4.35 (1H, dd, J = 5.8, 7.0 Hz), 4.48 (1H, d, J = 14.4 Hz), 6.20 (1H, s), 6.58 (1H, d, J = 1.8 Hz), 6.96-7.38 (6H, m).

EJEMPLO 7

Acido 2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-neopentil-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acético



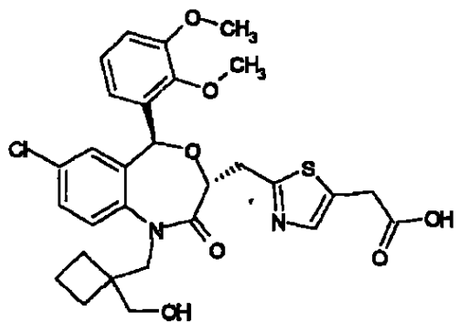
De conformidad con una manera similar a la del ejemplo 1, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 3.34 (1H, d, J = 13.5 Hz), 3.46 (1H, dd, J = 7.2, 15.0 Hz), 3.57 (1H, dd, J = 6.0, 15.0 Hz), 3.62 (3H, s), 3.84 (2H, s), 3.88 (3H, s), 4.33 (1H, dd, J = 6.0, 7.2 Hz), 4.50 (1H, d, J = 13.5 Hz), 6.31 (1H, s), 6.56 (1H, d, J = 2.1 Hz), 6.90-7.00 (1H, m), 7.10-7.20 (2H, m), 7.26 (1H, d, J = 8.7 Hz), 7.30 (1H, d, J = 2.1, 8.7 Hz),7.47 (1H, s).

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EJEMPLO 8

Acido {2-[((3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-{[1-(hidroximetil)ciclobutil]metil}-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)metil]-1,3-tiazol-5-il}acético

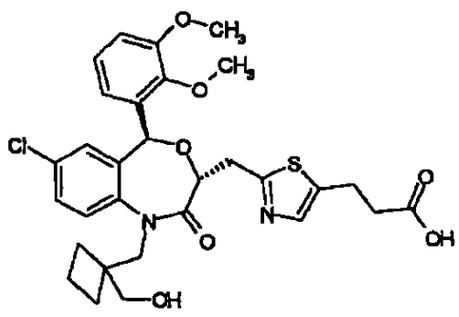


De conformidad con una manera similar a la del ejemplo 1, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 1.33-1.55 (2H, m), 1.76-1.94 (3H, m), 1.96-2.12 (1H, m), 3.41-3.78 (9H, m), 3.83 (2H, s), 3.87 (3H, s), 4.34 (1H, dd, J = 6.0, 6.9 Hz), 4.58 (1H, d, J = 14.4 Hz), 6.08 (1H, s), 6.57 (1H, d, J = 2.1 Hz), 6.95 (1H, dd, J = 1.8, 7.8 Hz), 7.07-7.18 (2H, m), 7.33-7.42 (2H, m), 7.48 (1H, s).

EJEMPLO 9

Acido 3-{2-[((3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-{[1-(hidroximetil)ciclobutil]metil}-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)metil]-1,3-tiazol-5-il}propiónico



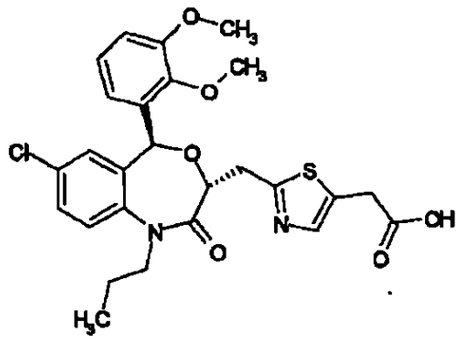
De conformidad con una manera similar a la del ejemplo 5, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 1.34-1.55 (2H, m), 1.77-1.95 (3H, m), 1.98-2.10 (1H, m), 2.68 (2H, t, J = 7.5 Hz), 3.11 (2H, t, J = 7.5 Hz), 3.42 (1H, dd, J = 6.9, 15.0 Hz), 3.50-3.82 (7H, m), 3.89 (3H, s), 4.34 (1H, t, J = 6.41 Hz), 4.58 (1H, d, J = 14.32 Hz), 6.09 (1H, s), 6.58 (1H, d, J = 2.1 Hz), 6.98 (1H, dd, J = 1.8, 8.1 Hz), 7.09 (1H, dd, J = 1.5,7.8 Hz), 7.17 (1H, t, J = 8.1 Hz), 7.35-7.43 (3H, m).

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EJEMPLO 10

Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1-propil-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acético



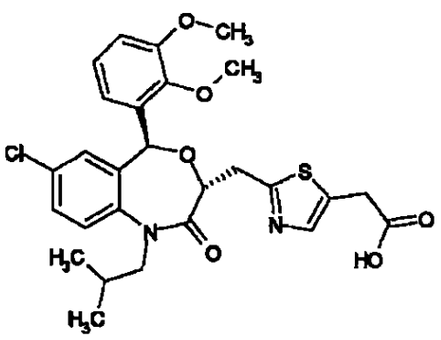
De conformidad con una manera similar a la del ejemplo 1, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.96 (3H, t, J = 7.5 Hz), 1.57-1.81 (2H, m), 3.43-3.63 (6H, m), 3.84 (2H, s), 3.87 (3H, s), 4.30-4.52 (2H, m), 6.11 (1H, s), 6.60 (1H, d, J = 1.8 Hz), 6.91-7.36 (5H, m), 7.49 (1H, s)

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EJEMPLO 11

Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-isobutil-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acético



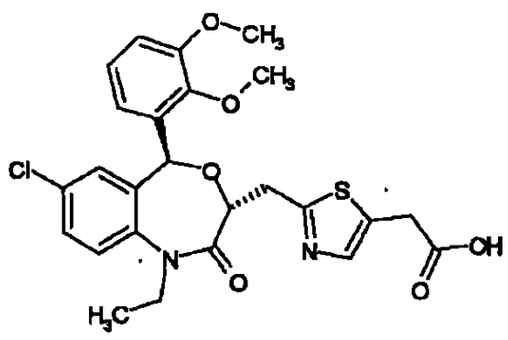
De conformidad con una manera similar a la del ejemplo 1, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.92 (3H, d, J = 6.4 Hz), 1.01 (3H, d, J = 6.8 Hz), 1.95-2.08 (1H1 m), 3.32-3.62 (6H, m), 3.82 (2H, s), 3.87 (3H, s), 4.31-4.40 (2H, m), 6.21 (1H, s), 6.59 (1H, d, J = 2.3 Hz), 6.92-7.35 (5H, m), 7.49 (1H, s).

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EJEMPLO 12

Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-etil-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acético



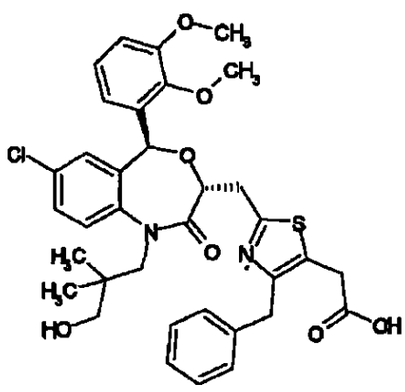
De conformidad con una manera similar a la del ejemplo 1, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 1.26 (3H, t, J = 7.2 Hz), 3.43-3.64 (6H, m), 3.84 (2H, s), 3.87 (3H, s), 4.33 (1H, t, J = 6.0 Hz), 4.49-4.62 (1H, m), 6.08 (1H, s), 6.60 (1H, d, J = 1.8 Hz), 6.91-7.36 (5H, m), 7.48 (1H, s).

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EJEMPLO 13

Acido (4-bencil-2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acético

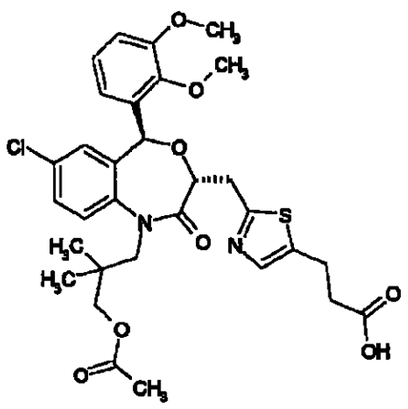


De conformidad con una manera similar a la del ejemplo 1, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 3.15 (1H, d, J = 11.7 Hz), 3.32 (1H, d, J = 14.4 Hz), 3.41 (1H, dd, J = 7.5, 14.7 Hz), 3.53 (1H, dd, J = 6.3, 14.7 Hz), 3.60 (3H, s), 3.62 (1H, d, J = 11.7 Hz), 3.76 (2H, s), 3.87 (3H, s), 4.00 (2H, s), 4.32-4.38 (1H, m), 4.42 (1H, d, J = 14.4 Hz), 6.17 (1H, s), 6.55 (1H, d, J= 2.4 Hz), 6.95 (1H, dd, J= 2.1, 7.2 Hz), 7.02-7.30 (8H, m), 7.32 (1H, dd, J = 2.4, 8.7 Hz).

EJEMPLO 14

Acido 3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)propiónico



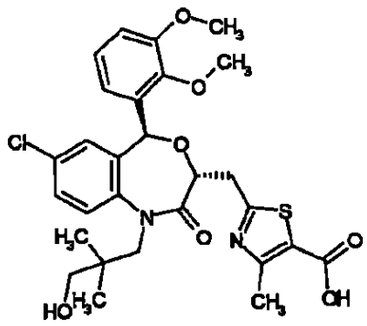
A una solución de ácido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)propiónico (0.5 g, 0.849 mmoles) obtenido en el ejemplo 5 en THF (10 ml), se añadió piridina (0.34 ml, 4.24 moles) a temperatura ambiente y después se añadió gota a gota cloruro de acetilo (0.18 ml, 2.55 mmoles). La mezcla se agitó durante 2.5 horas. Después se añadió agua (5 ml), la mezcla se agitó a temperatura ambiente durante 19 horas y la solución de reacción se extrajo con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener ácido 3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-

7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)propiónico (0.5 g, 0.792 mmoles, 93%) como polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.23 (3H, s), 2.02 (3H, s), 2.68 (2H, t, J = 7.5 Hz), 3.10 (2H, t, J = 7.5 Hz), 3.42 (1H, dd, J = 7.2, 15.0 Hz), 3.53 (1H, d, J = 14.1 Hz), 3.54 (1H, dd, J = 6.3, 15.0 Hz), 3.61 (3H, s), 3.73 (1H, d, J = 11.1 Hz), 3.85 (1H, d, J = 11.1 Hz), 3.88 (3H, s), 4.32 (1H, dd, J = 6.3,7.2 Hz), 4.56 (1H, d, J = 14.1 Hz), 6.29 (1H, s), 6.59 (1H, d, J = 2.1 Hz), 6.96 (1H, dd, J = 2.1, 7.8 Hz), 7.06-7.26 (2H, m), 7.27 (1H, d, J = 8.7 Hz), 7.31 (1H, dd, J = 2.1, 8.7 Hz), 7.35 (1H, s).

EJEMPLO 15

Acido 2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-{3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil)-4-metil-1,3-tiazol-5-carboxílico



(1) Se añadió DMF(0.01 ml) a una solución de ácido

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2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acético (3 g, 6.49 mmoles) y cloruro de tionilo (2.3 g, 19.5 mmoles) en THF (10 ml). La solución de reacción se agitó a temperatura ambiente durante 1 hora y después se concentró bajo presión reducida. El residuo se disolvió en THF (10 ml) y se añadió gota a gota a una solución de sulfuro de hidrógeno en piridina (30 ml). La solución de reacción se agitó a 0°C durante 1 hora y después se diluyó con ácido sulfúrico 2.5 M. El producto se extrajo con acetato de etilo (50 ml), se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio, y después se concentró bajo presión reducida para obtener ácido [(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-I,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]tio-S-acético (6.53 g) como polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.02 (3H, s), 2.03 (3H, s), 3.11 (1H, dd, J = 6.2, 16.4 Hz), 3.33 (1H, dd, J = 7.0, 16.4 Hz), 3.54 (1H, d, J = 14.0 Hz), 3.61 (3H, s), 3.72 (1H, d, J = 11.4 Hz), 3.85 (1H, d, J = 11.4 Hz), 3.89 (3H, s), 4.37 (1H, dd, J = 6.2, 7.0 Hz), 4.56 (1H, d, J = 14.0 Hz), 6.25 (1H, s), 6.64 (1H, d, J = 1.8 Hz), 6.96-7.35 (5H, m).

(2) Una solución de ácido [(3R,5S)-1-(3-acetoxi-

2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]tio-5-acético (1 g, 1.87 mmoles) obtenido en el ejemplo 15-(1), trietilamina (0.41 g, 4.04 mmoles) y 2-cloroacetoacetato de metilo (0.31 g, 2.06 mmoles) en éter (10 ml) se calentó a reflujo durante 2 horas. Después de que se añadió agua a la solución de reacción, la mezcla se extrajo con acetato de etilo (50 ml), se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (2:1)] para obtener 2-({2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]acetil}tio)-3-oxobutanoato de metilo (0.9 g, 1.38 mmoles, 74%) como polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.02 (3H, s), 2.02 (3H, s), 2.18 (3H, s), 3.14-3.26 (2H, m), 3.53 (1H, d, J= 14.4 Hz), 3.61 (3H, s), 3.72 (1H, d, J = 12.0 Hz), 3.74 (9/10 x 3H, s), 3.78 (1/10 x 3H, s), 3.85 (1H, d, J = 12.0 Hz), 3.89 (3H, s), 4.43 (1H, t, J = 6.4 Hz), 4.54 (1H, d, J = 14.4 Hz), 5.50 (1/10 x 3H, s), 6.26 (1H, s), 6.62 (1H, d, J = 1.8 Hz), 6.96-7.35 (5H, m).

(3) Una solución de 2-({2-[(3R,5S)-1-(3-acetoxi-

2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]acetil}tio)-3-oxobutanoato de metilo (0.8 g, 1.23 mmoles) obtenido en el ejemplo 15-(2) y acetato de amonio (0.33 g, 4.32 mmoles) en ácido acético (5 ml) se calentó a reflujo durante 1 hora. La solución de reacción se diluyó con acetato de etilo (50 ml), se lavó con una solución acuosa saturada de bicarbonato de sodio y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (3:2)]para obtener 2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-4-metil-1,3-tiazol-5-carboxilato de metilo (0.62 g, 0.982 mmoles, 80%) como polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.03 (3H, s), 2.03 (3H, s), 2.65 (3H, s), 3.421 (1H, dd, J = 7.0, 14.8 Hz), 3.53 (1H, d, J = 14.0 Hz), 3.56 (1H, dd, J = 6.0, 14.8 Hz), 3.62 (3H, 5),3.72 (1H, d, J = 11.4 Hz), 3.86 (3H, 5),3.86 (1H, d, J = 11.4 Hz), 3.89 (3H, s), 4.31 (1H, dd, J = 6.0, 7.0 Hz), 4.56 (1H, d, J = 14.0 Hz), 6.30 (1H, s), 6.61 (1H, d, J = 2.2 Hz), 6.96-7.37 (5H, m).

(4) Una mezcla de 2-{[(3R,5S)-1-(3-acetoxi-2,2-

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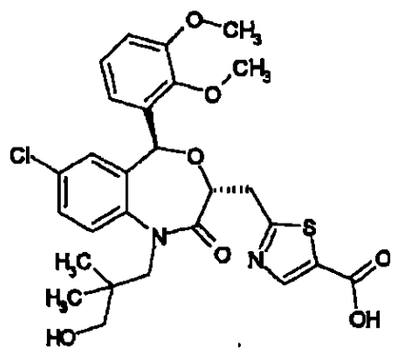
dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-4-metil-1,3-tiazol-5-carboxilato de metilo (0.4 g, 0.634 mmoles) obtenido en el ejemplo 15-(3), una solución acuosa 1 N de hidróxido de sodio (2 ml) y etanol (4 ml) se agitó a 60°C durante 30 minutos. Esta mezcla se diluyó con agua (50 ml), se acidificó y después se extrajo dos veces con acetato de etilo (50 ml). Los extractos se lavaron con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio, y después se concentró bajo presión reducida. El residuo se recristalizó a partir de etanol-hexano (1:1) para obtener ácido 2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-4-metil-1,3-tiazol-5-carboxílico (0.15 g, 0.261 mmoles, 41%) como un cristal prismático incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.66 (3H, s), 1.04 (3H, s), 2.65 (3H, s), 3.16 (1H, d, J = 12.0 Hz), 3.40 (1H, d, J = 14.1 Hz), 3.43 (1H, dd, J = 6.9, 14.4 Hz), 3.55 (1H, dd, J = 5.7, 14.1 Hz), 3.62 (1H, d, J = 12.0 Hz), 3.62 (3H, s), 3.90 (3H, s),4.32 (1H, dd, J = 5.7, 6.9 Hz), 4.47 (1H, d, J = 14.1 Hz), 6.21 (1H, s), 6.59 (1H, s), 6.99-7.38 (5H, m).

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EJEMPLO 16

Acido 2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-carboxílico



(1) A una solución de ácido 2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acético (10 g, 9.2 mmoles) en DMF (100 ml),se añadieron sal de amonio de 1-hidroxi-1H-benzotriazol (4.1 g, 26.9 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (5.16 g, 26.9 mmoles). Después de que la mezcla se agitó a temperatura ambiente durante 13 horas, se añadió agua (50 ml) y la mezcla se diluyó con acetato de etilo (350 ml). La capa orgánica se lavó con ácido clorhídrico 1 N, solución acuosa saturada de bicarbonato de sodio, agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener acetato de 3-[(3R,5S)-3-(2-amino-2-oxoetil)-7-cloro-5-(2,3-

dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (10.0 g) como polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.01 (3H, s), 2.03 (3H, s), 2.68 (1H, dd, J = 5.7, 14.7 Hz), 2.87 (1H, dd, J = 7.5, 14.7 Hz), 3.54 (1H, d, J = 13.8 Hz), 3.61 (3H, s), 3.73 (1H, d, J = 11.1 Hz), 3.86 {1H, d, J = 11.1 Hz), 3.89 (3H, s}, 4.39 (1H, dd, J = 5.7,7.5 Hz), 4.56 (1H, d, J = 13.8 Hz), 5.46 (1H, br), 5.95 (1H, br), 6.26 (1H, s), 6.64 (1H, d, J = 2.4 Hz), 6.91-7.01 (1H, m), 7.15-7.24 (2H, m), 7.31 (1H, d, J = 8.4 Hz), 7.35 (1H, dd, J = 2.4, 8.4 Hz).

(2) Una solución de acetato de 3-[(3R,5S)-3-(2-amino-2-oxoetil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (10.8 g, 20.8 mmoles) obtenido en el ejemplo 16-(1) y un reactivo de Lawesson (10.1 g, 24.8 mmoles) en THF (100 ml) se calentó a reflujo durante 1 hora con agitación. Después de reposar para enfriar a temperatura ambiente, una solución acuosa de bicarbonato de sodio (20 ml) se añadió y la mezcla se agitó durante 30 minutos. La solución de reacción se extrajo con acetato de etilo (800 ml), se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de

etilo (1:1)] para obtener acetato de 3-[(3R,5S)-3-(2-amino-2-tioxoetil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (5.14 g) como un cristal blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.01 (3H, s), 2.03 (3H, s), 3. 08 (1H, dd, J = 5.4, 13.5 Hz), 3.31 (1H, dd, J = 7.5, 13.5 Hz), 3.55 (1H, d, J = 14.1 Hz), 3.55 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.72 (1H, d, J = 11.4 Hz), 3.86 (1H, d, J = 11.4 Hz), 3.89 (3H, s), 4.46 (1H, dd, J = 5.4, 7.5 Hz), 4.53 (1H, d, J = 14.1 Hz), 6.26 (1H, s), 6.65 (1H, d, J = 2.4 Hz)(6.91-7.01 (1H, m), 7.15-7.24 (2H, m), 7.31 (1H, d, J = 8.7 Hz), 7.36 (1H, dd, J = 2.4, 8.7 Hz), 7.49 (1H, br), 7.64 (1H, br)

(3) Se añadió ácido acético (0.13 ml, 2.34 mmoles) a una suspensión de sal de potasio de 2-cloro-3-oxopropionato de etilo (0.42 g, 2.24 mmoles) en isopropanol (10 ml) y la mezcla se agitó durante 30 minutos. Al mismo se añadió 3-[(3R,58S-3-(2-amino-2-tioxoetil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (1.0 g, 1.87 mmoles) obtenido en el ejemplo 16-(2) y la mezcla se calentó a reflujo durante 30 horas con agitación. Después de reposar hasta enfriarse, se añadió agua (5 ml) a la solución de reacción, seguido por extracción con acetato de etilo (200 ml). La capa orgánica se

lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (7:3-65:35)] para obtener 2-{[(3R,5S)-1-[3-acetoxi-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-caboxilato de etilo (0.6 g) como polvo no cristalino incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 1.31 (3H, t, J = 7.2 Hz), 2.03 (3H, s), 2.82 (1H, dd, J = 5.7, 16.8 Hz), 2.92 (1H, dd, J = 7.5, 16.8 Hz), 3.54 (1H, d, J = 14.1 Hz), 3.62 (3H, s), 3.72 (1H, d, J = 11.1 Hz), 3.85 (1H,.d, J = 11.1 Hz), 3.87 (3H, s), 4.12 (2H, q, J = 7.2 Hz), 4.19 (1H, dd, J = 5.7, 7.5 Hz), 4.57 (1H, d, J = 14.1 Hz), 6.28 (1H, s), 6.53-6.55 (1H, m), 6.89-7.40 (5H, m), 8.70 (1H, s).

(4) Se añadió carbonato de potasio (0.26 g, 1.91 mmoles) a una solución de 2-{[(3R,5S)-1-[3-acetoxi-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-caboxilato de etilo (0.6 g, 0.95 mmoles) obtenido en el ejemplo 16-(3) en metanol (6 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. Se añadió agua (3 ml) a

la solución de reacción, seguido por extracción con acetato de etilo (80 ml). La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (67:33-3:2)] para obtener 2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropilo)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil-1,3-tiazol-5-carboxilato de metilo (0.3 g) como polvo no cristalino incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 3.07-3.21 (1H, m), 3.38 (1H, d, J = 14.1 Hz} , 3.58-3.70 (1H, m), 3.61 (3H, s), 3.73 (2H, d, J = 6.6 Hz), 3.85 (3H, s), 3.88 (3H, s), 4.48 (1H, d, J = 14.1 Hz), 4.53 (1H, t, J = 6.6 Hz), 6.17 (1H, s), 6.52-6.55 (1H, m), 6.90-7.10 (2H, m), 7.07-7.20 (1H, m), 7.26-7.40 (2H, m), 8.71 (1H, s).

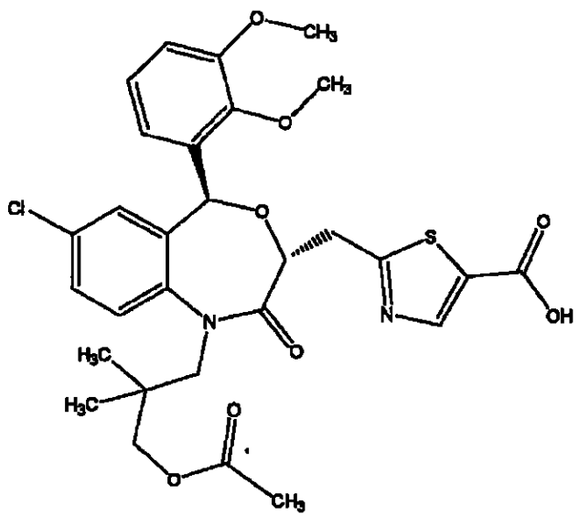
(5) Una mezcla de 2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]rnetil-1,3-tiazol-5-carboxilato de metilo (0.3 g, 0.52 mmoles) obtenido en el ejemplo 16-(4), en una solución acuosa de hidróxido de sodio (1 ml) y etanol (5 ml) se agitó a temperatura ambiente durante 8 horas. Después de que esta mezcla se acidificó con

ácido clorhídrico 1 N (1.2 ml), se añadió acetato de etilo (70 ml) a la misma. La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El cristal resultante se lavó con hexano para obtener ácido 2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-carboxílico (0.19 g) como un cristal blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.66 (3H, s), 1.05 (3H, s), 3.19 (1H, d, J = 12.3 Hz), 3.40 (1H, d, J = 14.1 Hz), 3.58-3.78 (3H, m), 3.61 (3H, s), 3.87 (3H, s), 4.47 (1H, d, J = 14.1 Hz), 4.57 (1H, t, J = 6.0 Hz), 6.18 (1H, s), 6.56 (1H, s), 6.90-7.01 (2H, m), 7.12 (1H, t, J = 7.8 Hz), 7.30-7.40 (2H, m), 8.76 (1H, s).

EJEMPLO 17

Acido 2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-carboxílico



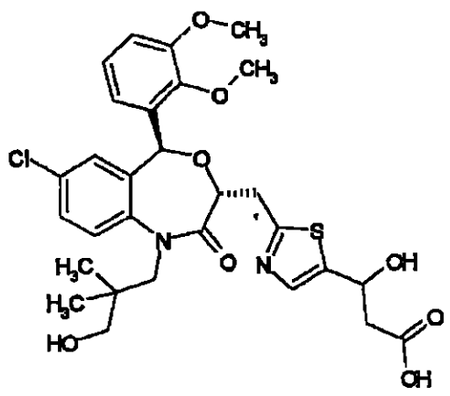
Después de que se añadió piridina (0.9 ml, 8.91 mol) a una solución de ácido 2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-acético (1.0 g, 1.78 mmoles) obtenido en el ejemplo 16 en THF(10 ml) a temperatura ambiente, se añadió gota a gota cloruro de acetilo (0.38 ml, 5.35 mmoles) y la mezcla se agitó durante 1 hora. A la misma se añadieron piridina (0.3 ml, 3.71 mmoles) y después cloruro de acetilo (0.1 ml, 1.41 mmoles) y la mezcla se agitó posteriormente durante 30 minutos. Después de que se añadió agua (5 ml), la mezcla se agitó a temperatura ambiente durante 19 horas y la solución de reacción se

extrajo con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener ácido 2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-carboxílico (0.76 g) como un polvo no cristalino café pálido.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 2.03 (3H, s), 3.42-3.63 (3H, m), 3.63 (3H, s), 3.73 (1H, d, J = 11.1 Hz), 3.70-3.90 (1H, m), 3.85 (1H, d, J = 11.1 Hz), 3.89 (3H, s), 4.55 (1H, d, J = 14.1 Hz), 4.50-4.60 (1H, m), 6.29 (1H, s), 6.63 (1H, d, J = 2.7 Hz), 6.98 (1H, dd, J = 1.5, 8.1 Hz), 7.08 (1H, dd, J = 1.5, 8.1 Hz), 7.17 (1H, t, J = 8.1 Hz), 7.29 (1H, d, J = 9.0 Hz), 7.34 (1H, dd, J = 2.7, 9.0 Hz), 8.76 (1H, s).

EJEMPLO 18

Acido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-hidroxipropiónico



(1) Se añadió 1,1'-Carbonildiimidazol (0.24 g, 1.49 mol) a una solución de ácido 2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-carboxílico (0.75 g, 1.24 mmoles) obtenido en el ejemplo 17 en THF (10 ml) a temperatura ambiente y la mezcla se agitó durante 1 hora. Se añadieron monoetilmalonato de potasio (0.23 g, 1.37 mmoles) y cloruro de magnesio (0.13 g, 1.37 mmoles) y la mezcla se agitó a 55°C durante 1 hora. Después de reposar hasta enfriarse, se añadió ácido clorhídrico 1 N (3 ml) y la mezcla se extrajo con acetato de etilo (150 ml). La capa orgánica se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El

residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (67:33-1:1)] para obtener 3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-oxopropionato de etilo (0.59 g, 0.88 mmoles, 71%) como polvo no cristalino incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.03 (3H, s), 1.26 (3H, t, J = 7.5 Hz), 2.03 (3H, s), 3.54 (1H, d, J = 14.1 Hz), 3.58-3.80 (2H, m), 3.60 (3H, s), 3.73 (1H, d, J = 10.8 Hz), 3.84 (1H, d, J = 10.8 Hz), 3.87 (3H, s), 3.93 (1Hr d, J = 15.9 Hz), 4.00 (1H, d, J = 15.9 Hz), 4.12 (2H, q, J = 7.5 Hz), 4.50 (1H, t, J = 6.6 Hz), 4.54 (1H, d, J = 14.1 Hz), 6.28 (1H, s), 6.56 (1H, s), 6.89-7.00 (2H, m), 7.10 (1H, t, J=7.8Hz), 7.30-7.34 (2H, m), 8.74 (1H, s).

(2) Una suspensión de 3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-oxopropionato de etilo (0.59 g, 0.88 mmoles) obtenido en el ejemplo 18-(1) en etanol (20 ml) se enfrió a -20°C y se añadió borhidruro de sodio (36 mg, 0.96 mmoles) a la misma. Después de agitarse durante 2 horas, se añadió una solución acuosa saturada de cloruro de amonio (5 ml) y la mezcla se extrajo con acetato de etilo (150 ml). La capa orgánica se

lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (55:45-35:65)] para obtener 3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-hidroxipropionato de etilo (0.49 g) como polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.92 (3H, s), 0.97 (3H, s), 1.26 (3H, t, J = 7.2 Hz), 2.04 (3H, s), 2.77 (1H, dd, J = 5.1, 15.9 Hz), 2.94 (1H, dd, J = 9.0, 15.9 Hz), 3.05-3.21 (2H, m), 3.42 (1H, d, J = 14.1 Hz), 3.62 (3H, s), 3.66 (1H, d, J = 11.7 Hz), 3.82 (1H, d, J = 11.7 Hz), 3.89 (3H, s), 4.12 (2H, q, J = 7.2 Hz), 4.42 (1H, d, J = 14.1 Hz), 4.30-4.52 (1H, m), 4.62-4.71 (1H, m), 5.62-5.80 (1H, m), 6.26 (1H, s), 6.62 (1H, d, J = 2.1 Hz), 6.98 (1H, dd, J = 2.4,7.2 Hz), 7.10-7.26 (3H, m), 7.30 (1H, dd, J = 2.1, 8.7 Hz), 8.55 (1H, s).

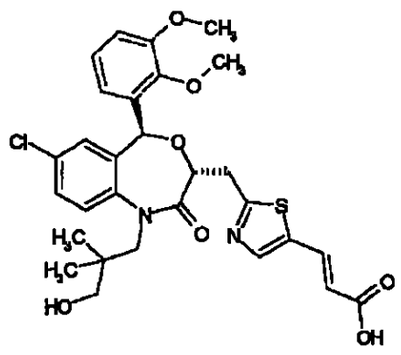
(3) Una mezcla de 3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-hidroxipropionato de etilo (0.06 g, 0.09 mmoles) obtenido en el ejemplo 18-(2), una solución acuosa 1N de hidróxido de sodio (0.5 ml) y etanol (1 ml) se agitó a temperatura

ambiente durante 2 horas. Esta mezcla se acidificó con ácido clorhídrico 1 N (0.6 ml) y se añadió acetato de etilo (40 ml) a la misma. La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El cristal resultante se lavó con hexano para obtener ácido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-hidroxipropiónico (0.05 g) como un cristal blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.66 (3H, s), 1.00 (3H, s), 2.73 (1H, dd, J = 5.1, 16.2 Hz), 2.81 (1H, dd, J = 8.4, 16.2 Hz), 3.14 (1H, d, J = 12.0 Hz), 3.19 (1H, dd, J = 5.4, 14.1 Hz), 3.36 (1H, d, J = 14.1 Hz), 3.48 (1H, dd, J = 7.8, 14.1 Hz), 3.60 (1H, d, J = 12.0 Hz), 3.61 (3H, s), 3.89 (3H, s), 4.41 (1H, d, J = 14.1 Hz), 4.50 (1H, dd, J = 5.4, 7.8 Hz), 5.64 (1H, dd, J = 5.1, 8.4 Hz), 6.18 (1H, s), 6.56 (1H, d, J = 2.1 Hz), 6.95-7.03 (2H, m), 7.16 (1H, t, J = 7.8 Hz), 7.29 (1H, d, J = 9.0 Hz), 7.35 (1H, dd, J = 2.1, 9.0 Hz), 8.59 (1H, s).

EJEMPLO 19

Acido (2E)-3-(2-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acrílico



(1) Trietilamina (0.11 ml, 0.77 mmoles) y cloruro de metansulfonilo (0.05 ml, 0.68 mmoles) se añadieron a una solución de 3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-hidroxipropionato de etilo (0.4 g, 0.59 mmoles) obtenido en el ejemplo 18-(2) en THF (5 ml) bajo enfriamiento con hielo y la mezcla se agitó durante 1 hora. Trietilamina (0.11 ml, 0.77 mmoles) y cloruro de metansulfonilo (0.05 ml, 0.68 mmoles) se añadieron adicionalmente a la misma y la mezcla se agitó durante 1 hora. Después, se añadió DBU (0.12 ml, 0.77 mmoles) a la misma y la mezcla se agitó durante 1 hora. Después, se añadió agua (10 ml) a la misma y la mezcla se extrajo con acetato de etilo (150 ml). La capa orgánica se lavó con agua y una

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solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatogràfía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (63:37-52:48)]para obtener (2E)-3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acrilato de etilo (0.05 g) como polvo no cristalino incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.96 (3H, s), 1.05 (3H, s), 1.25 (3H, t, J = 7.2 Hz), 2.04 (3H, s), 3.40 (2H, d, J = 6.0 Hz), 3.54 (1H, d, J = 14.0 Hz), 3.61 (3H, s), 3.73 (1H, d, J = 11.0 Hz), 3.86 (1H, d, J = 11.0 Hz), 3.87 (3H, s), 4.19 (2H, q, J = 7.2 Hz), 4.37 (1H, t, J = 6.6 Hz), 4.57 (1H, d, J = 14.0 Hz), 6.18 (1H, d, J = 15.4 Hz), 6.28 (1H, s), 6.54 (1H, s), 6.88 (1H, dd, J = 1.4, 7.6 Hz), 6.92 (1H, dd, J = 1.4, 7.6 Hz), 7.05 (1H, t, J = 7.6 Hz), 7.23-7.38 (2H, m), 7.92 (1H, d, J = 15.4 Hz), 8.63 (1H, s).

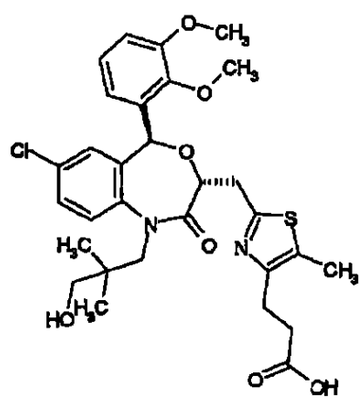
(2) Una mezcla de (2E)-3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acrilato de etilo (0.34 g, 0.52 mmoles) obtenido en el ejemplo 19-(1), una solución acuosa 1 N de hidróxido de sodio (1.5 ml) y etanol (7 ml) se agitó a 40°C durante 1 hora.

Después de reposar hasta enfriarse, esta mezcla se acidificó con ácido clorhídrico 1 N (1.7 ml) y se añadió acetato de etilo (160 ml). La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El cristal resultante se lavó con hexano para obtener ácido (2E)-3-(2-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acrílico (0.28 g) como un cristal amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.06 (3H, s), 3.19 (1H, d, J = 11.7 Hz), 3.37 (1H, d, J = 13.8 Hz), 3.39-3.45 (2H, m), 3.61 (3H, s), 3.67 (1H, d, J = 11.7 Hz), 3.86 (3H, s), 4.38 (1H, t, J = 7.2 Hz), 4.46 (1H, t, J = 13.8 Hz), 6.16 (1H, d, J = 15.6 Hz), 6.16 (1H, s), 6.53 (1H, d, J = 2.1 Hz), 6.88 (1H, dd, J = 1.5, 8.1 Hz), 6.93 (1H, dd, J = 1.5, 8.1 Hz), 7.08 (1H, t, J = 8.1 Hz), 7.29 (1H, d, J = 8.7 Hz), 7.33 (1H, dd, J = 2.1, 8.7 Hz), 8.02 (1H, d, J = 15.6 Hz), 8.66 (1H, s).

EJEMPLO 20

Acido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-5-metil-1,3-tiazol-4-il)propiónico



(1) Cloruro de pivaloilo (0.51 g, 4.23 mmoles) se añadió a una solución de ácido 2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acético (2 g, 3.85 mmoles) y trietilamina (0.41 g, 4.04 mmoles) en acetonitrilo (15 ml) a 0°C y la mezcla se agitó a 0°C durante 30 minutos. A la solución de reacción a 0°C, se añadió clorhidrato de (4S)-4-amino-5-oxohexanoate de metilo (0.83 g, 4.24 mmoles) y después se añadió gota a gota una solución de trietilamina (0.58 g, 5.77 mmoles) en acetonitrilo (2 ml).

Después de agitarse a temperatura ambiente durante 30 minutos, la solución de reacción se diluyó con acetato de etilo (50 ml), se lavó con ácido clorhídrico 0.1 N, una solución acuosa al 5% de sulfato ácido de potasio, una

solución acuosa de bicarbonato de sodio y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (1:2)] para obtener (48)-4-({2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]acetil}amino)-5-oxohexanoato de metilo (1.85 g, 2.80 mmoles, 73%) como polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.02 (3H, s), 1.78-1.90 (1H, m), 2.03 (3H, s), 2.23 (3H, s), 2.25-2.42 (3H, m), 2.70 (1H, dd, J = 5.4, 14.4 Hz), 2.89 (1H, dd, J = 7.8, 14.4 Hz), 3.54 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.67 (3H, s), 3.72 (1H, d, J ~ 11.1 Hz), 3.85 (1H, d, J = 11.1 Hz), 3.89 (3H, s), 4.36 (1H, dd, J = 5.4, 7.8 Hz), 4.54 (1H, d, J = 14.1 Hz), 4.56-4.65 (1H, m), 6.25 (1H, s), 6.60-6.64 (1H, br), 6.64 (1H, s), 6.97-7.32 (5H, m).

(2) Una solución de (48)-4-({2-[(3R,58)-1-(3-acetoxi-2,2-dımetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]acetil}amino)-5-oxohexanoato de metilo (0.51 g, 0.773 moles) obtenido en el ejemplo 20-(1) y reactivo de Lawesson (0.40 g, 1.00 mmoles) en THF (5 ml) se agitó a 70°C durante 1 hora. La solución de reacción se concentró bajo presión reducida y el residuo se

purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (1:1)] para obtener 3-(2-{[(3R,58)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il)metil}-5-metil-1,3-tiazol-4-il)propionato de metilo (0.31 g, 0.470 mmoles, 61%) como polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.03 (3H, s), 2.03 (3H, s), 2.34 (3H, s), 2.64 (2H, t, J = 7.4 Hz), 2.87 (2H, t, J = 7.4 Hz), 3.34 (1H, dd, J = 6.8, 15.0 Hz), 3.50 (1H, dd, J = 6.2, 15.0 Hz), 3.53 (1H, d, J = 14.2 Hz), 3.62 (3H, s), 3.63 (3H, s), 3.72 (1H, d, J = 11.0 Hz), 3.85 (1H, d, J = 11.0 Hz), 3.89 (3H, s), 4.27 (1H, dd, J = 6.2, 6.8 Hz), 4.56 (1H, d, J = 14.2 Hz), 6.29 (1H, s), 6.60 (1H, d, J = 1.8 Hz), 6.95-7.36 (5H, m).

(3) Una mezcla de 3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]metil}-5-metil-1,3-tiazol-4-il)propionato de metilo (0.2 g, 0.303 mmoles) obtenida en el ejemplo 20-(2), una solución acuosa 1 N de hidróxido de sodio (1 ml) y etanol (2 ml) se agitó a 60°C durante 30 minutos. Esta mezcla se diluyó con agua (50 ml), se acidificó, y se extrajo dos veces con acetato de etilo (50 ml). Este extracto se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio, y

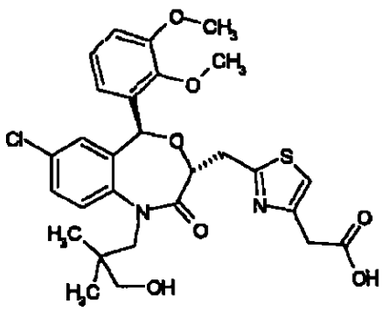
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después se concentró bajo presión reducida para obtener ácido 3-((2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)metil}-5-metil-1,3-tiazol-4-il)propiónico (0.18 g, 0.298 mmoles, 98%) como polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.33 (3H, s), 2.66-2.72 (2H, m), 2.83-2.89 (2H, m), 3.16 (1H, d, J = 11.8 Hz), 3.37 (1H, dd, J = 6.2, 15.4 Hz), 3.42 (1H, d, J = 14.6 Hz), 3.59 (1H, dd, J = 6.6, 15.4 Hz), 3.62 (3H, s), 3.63 (1H, d, J = 11.8 Hz), 3.90 (3H, s), 4.30 (1H, dd, J = 6.2, 6.6 Hz), 4.46 (1H, d, J = 14.6 Hz), 6.20 (1H, s), 6.60 (1H, d, J = 1.4 Hz), 6.97-7.39 (5H, m).

EJEMPLO 21

Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-4-il)acético



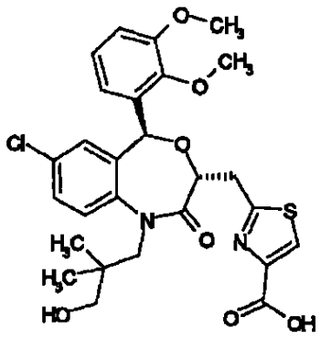
De conformidad con una manera similar a la del

ejemplo 16, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 3.17 (1H, d, J = 11.9 Hz), 3.41 (1H, d, J = 14.5 Hz), 3.48 (1H, dd, J = 6.5, 15.4 Hz), 3.60-3.71 (5H, m), 3.80 (2H, s), 3.90 (3H, s), 4.35 (1H, t, J = 6.5 Hz), 4.46 (1H, d, J = 14.5 Hz), 6.21 (1H, s), 6.60 (1H, s), 7.00 (1H, dd, J = 2.1, 7.7 Hz), 7.05 (1H, s), 7.11-7.22 (2H, m), 7.33-7.40 (2H, m).

EJEMPLO 22

Acido 2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-4-carboxílico



(1) Una solución de acetato de 3-[(3R,5S)-3-(2-amino-2-oxoetil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (3.0 g, 5.61 mmoles) obtenido en el ejemplo 16-(2) y 3-bromo-2-oxopropionato de etilo (0.79 ml, 6.28 mmoles) en etanol (30 ml) se calentó a reflujo durante 2 horas con agitación.

Después de reposar hasta reposo se añadió agua (15 ml) a la solución de reacción, seguido por extracción con acetato de etilo (300 ml). La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (3:2-1:1)] para obtener 2-{[(3R,5S)-1-[3-acetoxi-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-4-carboxilato de etilo (1.1 g) como polvo no cristalino incoloro de una primera fracción eluida, y 2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-4-carboxilato de etilo (2.0 g) como polvo incoloro de una segunda fracción diluida.

Primera fracción diluida

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.03 (3H, s), 1.37 (3H, t, J = 7.0 Hz), 2.03 (3H, s), 3.41-3.62 (3H, m), 3.61 (3H, s), 3.72 (1H, d, J = 11.0 Hz), 3.96 (1H, d, J = 11.0 Hz), 3.89 (3H, s), 4.27-4.40 (1H, m), 4.39 (2H, q, J = 7.0 Hz), 4.55 (1H, d, J = 14.0 Hz), 6.31 (1H, s), 6.59 (1H, d, J = 1.8 Hz), 6.98 (1H, dd, J = 2.0, 7.8 Hz), 7.08 (1H, dd, J = 2.0,7.8 Hz), 7.17 (1H, t, J = 7.8 Hz), 7.23-7.40 (2H, m),

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8.09 (1H, s).

Segunda fracción diluida

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 1.38 (3H, t, J = 7.0 Hz), 3.16 (1H, t, J = 11.8 Hz), 3.37 (1H, d, J = 25 14.4 Hz), 3.45-3.72 (3H, m), 3.62 (3H, s), 3.89 (3H, s), 4.05-4.15 (1H, m), 4.35 (1H, t, J = 7.0 Hz), 4.39 (2H, q, J = 7.0 Hz), 4.47 (1H, d, J = 14.4 Hz), 6.21 (1H, s), 6.56 (1H, d, J = 2.2 Hz), 6.99 (1H, dd, J = 1.8, 8.0 Hz), 7.07 (1H, dd, J = 1.8,8.0 Hz), 7.18 (1H, t, J = 8.0 Hz), 7.29 (1H, d, J= 8.4 Hz), 7.35 (1H, dd, J= 2.2,8.4 Hz), 8.09 (1H, s).

(2) Una mezcla de 2-{[(3R,5S)-1-[3-acetoxi-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-4-carboxilato de etilo (0.34 g, 0.52 mmoles) y 2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-4-carboxilato de etilo (2.0 g, 3.40 mmoles) obtenido en el ejemplo 22-(1), una solución acuosa 1 N de hidróxido de sodio (14.0 ml) y etanol (60 ml) se agitó a temperatura ambiente durante 5 horas. Esta mezcla se acidificó con ácido clorhídrico 1 N (14.5 ml) y se añadió acetato de etilo (380 ml) a la misma. La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. Al

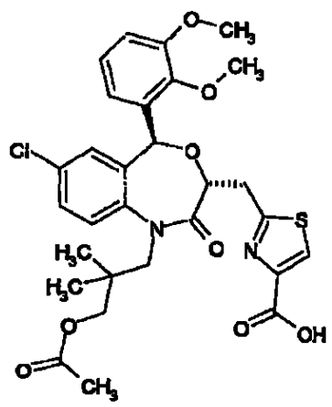
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residuo resultante se añadió éter dietílico (30 ml), una solución acuosa 1 N de hidróxido de sodio (14 ml) y agua (100 ml). La capa acuosa se lavó con éter dietílico (50 ml) y después se acidificó con ácido clorhídrico 1 N (14.5 ml) y se añadió acetato de etilo (380 ml) a la misma. La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener ácido 2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-4-carboxílico (2.9 g) como un polvo no cristalino amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 3.18 (1H, d, J = 12.0 Hz), 3.38 (1H, d, J = 13.8 Hz), 3.54 (1H, dd, J = 7.2,14.7 Hz), 3.56-3.68 (1H, m), 3.62 (3H, s), 3.89 (3H, s), 4.34 (1H, dd, J = 5.7, 7.2 Hz), 4.46 (1H, d, J = 13.8 Hz), 6.21 (1H, s), 6.57 (1H, d, J=2.1Hz), 6.98 (1H, dd, J = 1.5, 8.1 Hz), 7.06 (1H, dd, J = 1.5, 8.1 Hz), 7.17 (1H, t, J = 8.1 Hz), 7.29 (1H, d, J = 8.7 Hz), 7.35 (1H, dd, J = 2.1, 8.7 Hz), 8.18 (1H, s).

EJEMPLO 23

Acido 2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-4-carboxílico

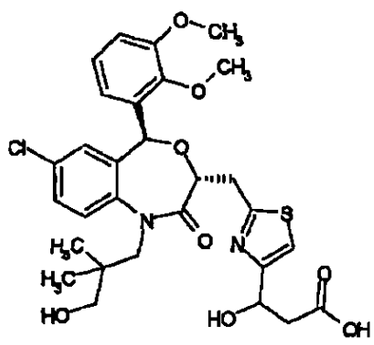


De conformidad con una manera similar a la del ejemplo 17, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.03 (3H, s), 2.03 (3H, 5 s), 3.45-3.66 (3H, m), 3.61 (3H, s), 3.72 (1H, d, J = 10.8 Hz), 3.85 (1H, d, J = 10.8 Hz), 3.89 (3H, s), 4.32 (1H, dd, J = 5.7, 7.2 Hz), 4.55 (1H, d, J = 13.8 Hz), 6.31 (1H, s), 6.60 (1H, d, J = 2.4 Hz), 6.98 (1H, dd, J = 1.5,7.8 Hz), 7.06 (1H, dd, J = 1.5, 7.8 Hz), 7.10-7.20 (1H, m), 7.27 (1H, d, J = 9.0 Hz), 7.32 (1H, dd, J = 2.4, 9.0 Hz), 8.18 (1H, s).

EJEMPLO 24

Acido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-4-il)-3-hidroxipropiónico

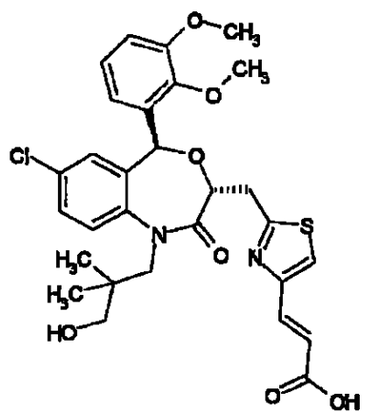


De conformidad con una manera similar a la del ejemplo 18, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 2.78-3.04 (2H, m), 3.16 (1H, d, J = 11.4 Hz), 3.39 (1H, d, J = 14.1 Hz), 3.40-3.70 (3H, m), 3.61 (3H, s), 3.89 (3H, s), 4.31 (1H, t, J = 6.6 Hz), 4.46 (1H, d, J = 14.1 Hz), 5.11-5.21 (1H, m), 6.20 (1H, s), 6.59 (1H, s), 6.96-7.02 (1H, m), 7.08-7.20 (3H, m), 7.29-7.41 (2H, m)

EJEMPLO 25

Acido (2E)-3-{2-[((3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)metil]-1,3-tiazol-4-il}acrílico



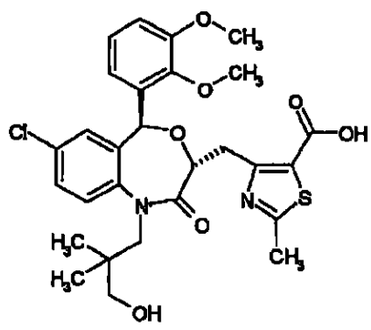
De conformidad con una manera similar a la del ejemplo 19, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.66 (3H, s), 1.06 (3H, s), 3.18 (1H, d, J = 12.0 Hz), 3.41 (1H, d, J = 13.8 Hz), 3.49 (1H, dd, J = 6.6, 15.3 Hz), 3.58-3.70 (2H, m), 3.63 (3H, s), 3.90 (3H, s), 4.40 (1H, t, J = 6.6 Hz), 4.48 (1H, d, J = 13.8 Hz), 6.23 (1H, s), 6.60 (1H, d, J = 2.4 Hz), 6.62 (1H, d, J = 15.3 Hz), 7.00 (1H, dd, J = 2.4, 7.2 Hz), 7.13-7.21 (2H, m), 7.30-7.41 (3H, m), 7.62 (1H, d, J = 15.3 Hz).

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EJEMPLO 26

Acido 4-[((3R,5S)-7-cloro-5-(2,3-dirnetoxifenil)-1-(3-hidroxi-2,2-dimetılpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)metil]-2-metil-1,3-tiazol-5-carboxílico



(1) Carbonilodiimizazol (3.7 g) se añadió a una suspensión de ácido 2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropıl)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acético (10 g) en THF (100 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. A la solución de reacción se añadió cloruro de magnesio (2.2 g) y monoetilmalonato de potasio (4.0 g) y la mezcla se agitó a 60°C durante 1 hora. La solución de reacción se diluyó con acetato de etilo (200 ml), se lavó con en ácido clorhídrico, una solución acuosa de bicarbonato de sodio y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener 4-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-S-(2,3-dimetoxifenil)-2-

oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]}-3-oxobutanoato de etilo (10.2 g) como un cristal blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.01 (3H, s), 1.27 (3H, s), 2.02 (3H, s), 2.96 (1H, dd, J = 5.0, 17.2 Hz), 3.27 (1H, dd, J = 7.8, 17.0 Hz), 3.42-3.57 (3H, m), 3.61 (3H, s), 3.69-3.82 (2H, m), 3.89 (3H, s), 4.18 (2H, q, J = 7.4 Hz), 4.41-4.57 (2H, m), 6.24 (1H, s), 6.63 (1H, s), 6.95-7.02 (1H, m), 7.15-7.20 (2H, m), 7.33-7.34 (4H, m)

(2) Se añadió cloruro de sulfurilo (0.23 ml) a una solución de 4-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]}-3-oxobutanoato de etilo (1.5 g) obtenido en el ejemplo 26-(1) en diclorometano (30 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. La solución de reacción se vació en agua, que se extrajo con cloroformo. La capa orgánica se concentró bajo presión reducida. Se añadió tioacetamida (0.21 g) y etanol (30 ml) al residuo y la mezcla se puso a reflujo durante la noche. La solución de reacción se concentró y el residuo se purificó por cromatografía en columna sobre gel de sílice para obtener 4-[((3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)metil}-2-metil-1,3-tiazol-5-carboxilato de etilo (0.80 g) como un cristal amorfo incoloro.

^{1}H-RMN (CD_3OD) δ: 0.93 (3H, s), 1.23 (3H, s), 1.27 (3H, t, J = 7.2 Hz), 2.03 (3H, s), 2.64 (3H, s), 3.51-3.57 (1H, m), 3.60 (3H, s), 3.67-3.85 (4H, rn), 3.87 (3H, s), 4.23 (2H, q, J z 7.2 Hz), 4.37-4.44 (2H, m), 6.26 (1H, s), 6.53 (1H, s), 6.87-6.99 (2H, m), 7.05-7.10 (1H, m), 7.16-7.18 (1H, m), 7.32-7.37(2H, m).

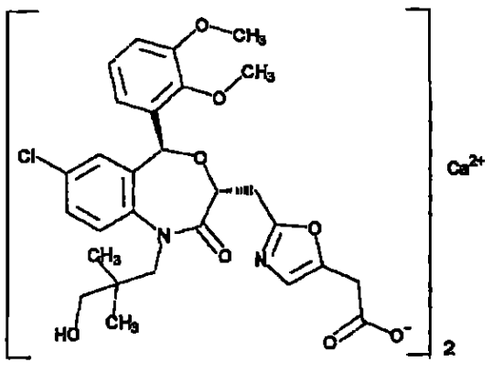
(3) Una mezcla de 4-[((3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)metil]-2-metil-1,3-tiazol-5-carboxilato de etilo (0.7 g) obtenido en el ejemplo 26-(2), una solución acuosa 2N de hidróxido de sodio (2 ml) y etanol (10 ml) se agitó a temperatura ambiente durante 30 minutos. Esta mezcla se diluyó con agua (50 ml), se acidificó y se extrajo dos veces con cloroformo (50 ml). Estos extractos se lavaron con una solución acuosa saturada de cloruro de sodio, se secaron sobre sulfato de magnesio, y después se concentraron bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener ácido 4-[((3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)metil]-2-metil-1,3-tiazol-5-carboxílico (0.19 g) como un cristal blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.04 (3H, s), 1.12 (3H, s), 1.14 (3H, s), 2.62 (3H, s), 3.12-3.16 (1H, m), 3.35-

3.40 (1H, m), 3.53 (3H, s), 3.62-3.68 (3H, m), 3.87 (3H, s), 4.41-4.50 (2H, m), 6.16 (1H, s), 6.53 (1H, s), 6.93-6.97 (2H, m), 7.09-7.14 (1H, m), 7.26-7.33(2H, m)

EJEMPLO 27

Sal de calcio de ácido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)acético



(1) Se añadió oxicloruro de fósforo (0.35 g, 2.33 mmoles) a una solución de 4-({2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]acetil}amino)-3-oxobutanoato de etilo (1 g, 1.55 mmoles) obtenido en el ejemplo 1-(3) en DMF (3 ml) y la mezcla se agitó a 70°C durante 1 hora. La solución de reacción se enfrió en un baño de hielo y una solución acuosa de bicarbonato de sodio (50 ml) se añadió a la misma. El producto de extrajo con acetato

de etilo (50 ml) dos veces, se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (3:2)] para obtener (2-{[(3R,5S)-1-(3-acetoxi- 2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)acetato de etilo (0.57 g, 0.906 mmoles, 58%) como polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.03 (3H, s), 1.26 (3H, t, J = 7.4 Hz), 2.03 (3H, s), 3.24 (1H, dd, J = 7.4, 15.8 Hz), 3.36 (1H, dd, J = 6.6, 15.8 Hz), 3.54 (1H, d, J = 14.0 Hz), 3.61 (3H, s), 3.68 (2H, s), 3.73 (1H, d, J = 11.4 Hz), 3.85 (1H, d, J = 11.4 Hz), 3.89 (3H, s), 4.18 (2H, q, J = 7.4 Hz), 4.44 (1H, dd, J = 6.6, 7.4 Hz), 4.58 (1H, d, J = 14.0 Hz), 6.30 (1H, s), 6.60 (1H, s), 6.85 (1H, s), 6.94-7.33 (5H, m).

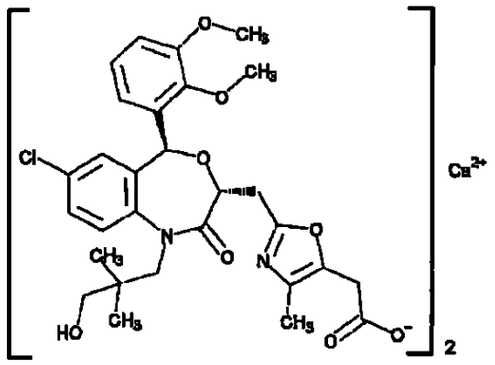
(2) Una mezcla de (2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)acetato de etilo (0.47 g, 0.747 mmoles) obtenido en el ejemplo 27-(1), una solución acuosa 1 N de hidróxido de sodio (2 mmoles) y etanol (5 ml) se agitó a 60°C durante 30 minutos. Esta mezcla se lavó con agua (5 ml), se acidificó y

se extrajo dos veces con acetato de etilo (50 ml). Estos extractos se lavaron con una solución acuosa saturada de cloruro de sodio, se secaron sobre sulfato de sodio, y después se concentraron bajo presión reducida para obtener ácido (2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)acético (0.42 g). Este se disolvió en etanol (6 ml) y se añadió una solución acuosa 1 N de hidróxido de sodio (0.75 ml) al mismo. La mezcla se concentró después bajo presión reducida. El residuo se disolvió en agua (2 ml) y se añadió una solución de cloruro de calcio (42 mg, 0.378 mmoles) en agua (0.5 ml). Los precipitados producidos se filtraron para obtener sal de calcio de ácido (2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)acético (0.29 g, 0.247 mmoles, 66%) como polvo incoloro.

^{1}H-RMN ($CDCl_3$-D_3OD (1:2)) δ: 0.81 (3H, s), 0.97 (3H, s), 3.19 (1H, d, J = 11.8 Hz), 3.22-3.29 (2H, m), 3.50 (1H, d, J = 11.8 Hz), 3.55 (2H, s), 3.60 (3H, s), 3.62 (1H, d, J = 13.4 Hz), 3.90 (3H, s), 4.40-4.47 (2H, m), 6.21 (1H, s), 6.55 (1H, d, J = 2.6 Hz), 6.78 (1H, s), 7.02-7.37 (5H, m).

EJEMPLO 28

Sal de calcio de ácido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-4-metil-1,3-oxazol-5-il)acético

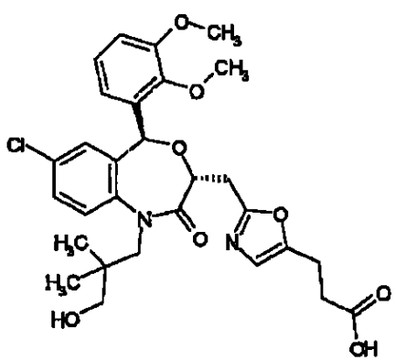


De conformidad con una manera similar a la del ejemplo 27, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$-CD_3OD (1:2)) δ: 0.83 (3H, s), 0.95 (3H, s), 2.05 (3H, s), 3.18-3.26 (3H, m), 3.44-3.68 (4H, m), 3.59 (3H, s), 3.89 (3H, s), 4.38-4.46 (2H, m), 6.20 (1H, s), 6.53 (1H, d, J = 2.2 Hz), 7.02-7.59 (5H, m).

EJEMPLO 29

Acido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)propiónico



(1) De conformidad con una manera similar a la del ejemplo 27-(1), se obtuvo 3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)propionato de metilo.

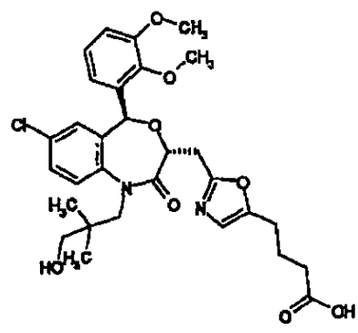
^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.03 (3H, s), 2.03 (3H, s), 2.64 (2H, t, J = 7.4 Hz), 2.96 (2H, t, J = 7.4 Hz), 3.21 (1H, dd, J = 7.0, 15.4 Hz), 3.33 (1H, dd, J = 6.6, 15.4 Hz), 3.54 (1H, d, J = 14.2 Hz), 3.61 (3H, s), 3.69 (3H, s), 3.73 (1H, d, J = 11.0 Hz), 3.85 (1H, d, J = 11.0 Hz), 3.89 (3H, s), 4.41 (1H, dd, J = 6.6, 7.0 Hz), 4.58 (1H, d, J = 14.2 Hz), 6.30 (1H, s), 6.60 (1H, s), 6.65 (1H, s), 6.95-7.33 (5H, m).

(2) Una mezcla de (2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)propionato de metilo (0.11 g, 0.175 mmoles) obtenido en el ejemplo 29-(1), una solución acuosa 1 N de hidróxido de sodio (0.5 ml) y etanol (2 ml) se agitó a 60°C durante 30 minutos. Esta se diluyó con agua (50 ml), se acidificó y después se extrajo dos veces con acetato de etilo (50 ml). Esta se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio, y después se concentró bajo presión reducida. El residuo se purificó por recristalización a partir de etanol-hexano (1:1) para obtener ácido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)propiónico (50 mg, 0.0873 mmoles, 50%) como polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 2.67 (2H, t, J = 7.0 Hz), 2.95 (2H, t, J = 7.0 Hz), 3.16 (1H, d, J = 12.8 Hz), 3.22 (1H, dd, J = 7.0, 15.8 Hz), 3.37 (1H, dd, J = 6.6, 15.8 Hz), 3.39 (1H, d, J = 15.4 Hz), 3.62 (.3H, s), 3.63 (1H, d, J = 12.8 Hz), 3.89 (3H, s), 4.44 (1H, dd, J = 6.6, 7.0 Hz), 4.48 (1H, d, J = 15.4 Hz), 6.19 (1H, s), 6.59 (1H, s), 6.68 (1H, s), 6.96-7.36 (5H, m)

EJEMPLO 30

Acido 4-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)butanoico

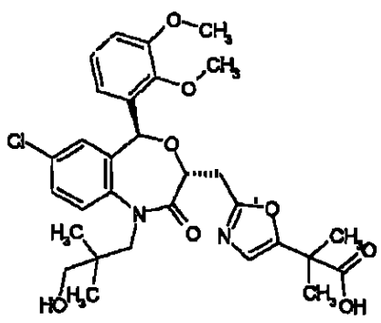


De conformidad con una manera similar a la del ejemplo 29, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.04 (3H, s), 1.95 (2H, quintuplete, J = 7.4 Hz), 2.38 (2H, t, J = 7.4 Hz), 2.69 (2H, t, J = 7.4 Hz), 3.16 (1H, d, J = 12.2 Hz), 3.21 (1H, dd, J = 6.6, 15.6 Hz), 3.38 (1H, dd, J = 7.0, 15.6 Hz), 3.40 (1H, d, J = 15.0 H:z), 3.61 (3H, s), 3.63 (1H, d, J = 12.2 Hz), 3.89 (3H, s), 4.42-4.52 (2H, m), 6.19 (1H, s), 6.58 (1H, s), 6.66 (1H, s), 6.95-7.36 (5H, m).

EJEMPLO 31

Acido 2-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)-2-metilpropiónico

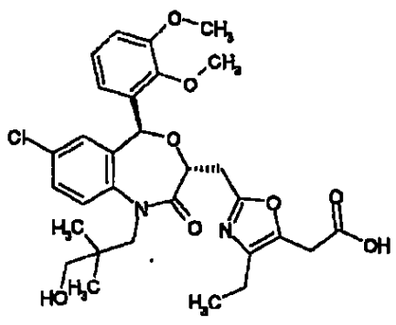


De conformidad con una manera similar a la del ejemplo 29, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.037 (3H, s), 1.56 (6H, s), 3.17 (1H, d, J = 11.6 Hz), 3.25 (1H, dd, J = 7.0, 15.8 Hz), 3.38 (3H, dd, J = 6.6, 15.8 Hz), 3.39 (1H, d, J = 14.0 Hz), 3.61 (3H, s), 3.62 (1H, d, J = 11.6 Hz), 3.88 (3H, s), 4.41 (1H, dd, J = 6.6, 7.0 Hz), 4.47 (1H, d, J = 14.0 Hz), 6.18 (1H, s), 6.57 (1H, s), 6.80 (1H, s), 6.95-7.53 (5H, m).

EJEMPLO 32

Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-4-etil-1,3-oxazol-5-il)acético



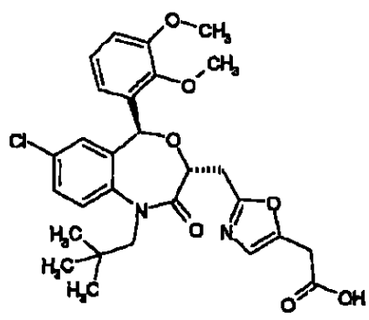
De conformidad con una manera similar a la del ejemplo 29, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.04 (3H, s), 1.16 (3H, t, J = 7.6 Hz), 2.43 (2H, q, J = 7.6 Hz), 3.17 (1H, d, J = 12.0 Hz), 3.26-3.30 (2H, m), 3.38 (1H, d, J = 14.4 Hz), 3.60 (3H, s), 3.62 (2H, s), 3.62 (1H, d, J = 12.0 Hz), 3.87 (3H, s), 4.39-4.50 (2H, m), 6.17 (1H, s), 6.57 (1H, d, J = 1.4 Hz), 6.93-7.39 (5H, m).

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EJEMPLO 33

Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-neopentil-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)acético

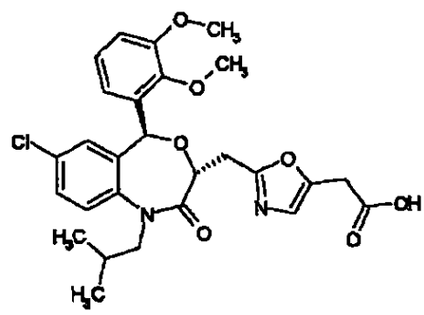


De conformidad con una manera similar a la del ejemplo 29, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (9H, s), 3.27 (1H, dd, J = 7.2, 15.6 Hz), 3.35 (1H, dd, J = 6.0, 15.6 Hz), 3.36 (1H, d, J = 13.8 Hz), 3.61 (3H, s), 3.71 (2H, s), 3.87 (3H, s), 4.44 (1H, dd, J = 6.0, 7.2 Hz), 4.50 (1H, d, J = 13.8 Hz), 6.29 (1H, s), 6.56 (1H, s), 6.88 (1H, s), 6.94 (1H, dd, J = 1.5, 7.8 Hz), 7.03 (1H, dd, J = 0.9, 7.8 Hz), 7.13 (1H, t, J = 7.8 Hz), 7.26-7.34 (2H, m).

EJEMPLO 34

Acido 2-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-isobutil-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)acético

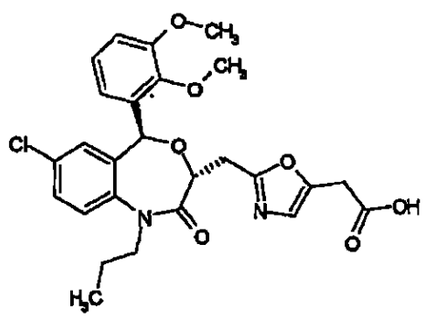


De conformidad con una manera similar a la del ejemplo 29, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.92 (3H, d, J = 6.6 Hz), 1.00 (3H, d, J = 6.9 Hz), 1.95-2.09 (1H, m), 3.32-3.41 (3H, m), 3.57 (3H, s), 3.69 (2H, s), 3.87 (3H, s), 4.37 (1H, t, J = 7.8, 13.8 Hz), 4.46 (1H, t, J = 6.3 Hz), 6.19 (1H, s), 6.60 (1H, d, J = 1.8 Hz), 6.90 (1H, s), 6.92-7.36 (5H, m).

EJEMPLO 35

Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1-propil-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)acético

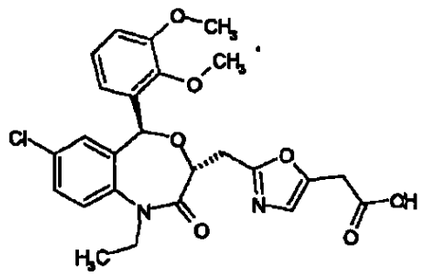


De conformidad con una manera similar a la del ejemplo 29, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, t, J = 7.5 Hz), 1.56-1.84 (2H, m), 3.23-3.54 (3H, m), 3.56 (3H, s), 3.69 (2H, s), 3.86 (3H, s), 4.40-4.52 (2H, m), 6.09 (1H, s), 6.60 (1H, d, J = 2.1 Hz), 6.90 (1H, s), 6.93-7.37 (5H, m).

EJEMPLO 36

Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-etil-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)acético

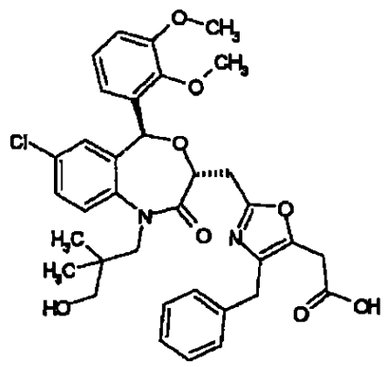


De conformidad con una manera similar a la del ejemplo 29, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 1.25 (3H, t, J = 7.2 Hz), 3.28 (1H, dd, J = 7.2, 15.6 Hz), 3.39 (1H, dd, J = 7.2, 15.6 Hz), 3.50-3.66 (4H, m), 3.69 (2H, s), 3.86 (3H, s), 4.45 (1H, t, J = 6.3 Hz), 4.48-4.62 (1H, m), 6.06 (1H, s), 6.61 (1H, d, J = 1.8Hz), 6.90 (1H, s), 6.92-7.37 (5H, m).

EJEMPLO 37

Acido (4-bencil-2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)acético

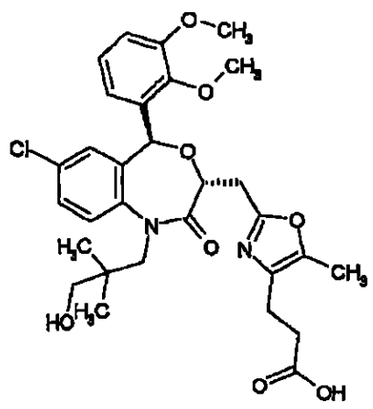


De conformidad con una manera similar a la del ejemplo 29, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 3.15 (1H, d, J = 12.6 Hz), 3.26 (2H, dd, J = 4.5,7.2 Hz), 3.35 (1H, d, J = 14.4 Hz), 3.51 (2H, d, J = 1.8 Hz), 3.59 (3H, s), 3.60 (1H, d, J = 12.6 Hz), 3.79 (2H, s), 3.86 (3H, s), 4.41 (1H, t, J = 7.2 Hz), 4.43 (1H, d, J = 14.4 Hz), 6.15 (1H, s), 6.55 (1H, d, J = 2.1 Hz), 6.93 (1H, dd, J = 1.5, 8.1 Hz), 6.98 (1H, dd, J = 1.5, 8.1 Hz), 7.08 (1H, t, J = 8.1 Hz), 7.13-7.26 (5H, m), 7.28 (1H, d, J = 9.0 Hz), 7.34 (1H, dd, J = 2.1, 9.0 Hz).

EJEMPLO 38

Acido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-5-metil-1,3-oxazol-4-il)propiónico



(1) Oxicloruro de fósforo (0.35 g, 2.33 mmoles) se añadió a una solución de (4S)-4-({2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]acetil}amino)-5-oxohexanoato de metilo (1 g, 1.55 mmoles) obtenido en el ejemplo 20-(1) en DMF (3 ml) y la mezcla se agitó a 80°C durante 1 hora. La solución de reacción se enfrió en un baño de hielo y se añadió una solución acuosa de bicarbonato de sodio (50 ml). El producto de extrajo dos veces con acetato de etilo (50 ml), se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (1:1)] para

obtener 3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]metil}-5-metil-1,3-oxazol-4-il)propionato de metilo (0.83 g, 1.29 mmoles, 83%) como polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.03 (3H, s), 2.03 (3H, s), 2.22 (3H, s), 2.57-2.62 (2H, m), 2.66-2.71 (2H, m), 3.19 (1H, dd, J = 7.2, 15.6 Hz), 3.25 (1H, dd, J = 6.0, 15.6 Hz), 3.54 (.1H, d, J = 13.8 Hz), 3.61 (3H, s), 3.64 (3H, s), 3.74 (1H, d, J = 11.1 Hz), 3.84 (1H, d, J = 11.1 Hz), 3.89 (3H, s), 4.36 (1H, dd, J = 6.0,7.2 Hz), 4.57 (1H, d, J = 13.8 Hz), 6.29 (1H, s), 6.59 (1H, d, J = 1.8 Hz), 6.95-7.34 (5H, m).

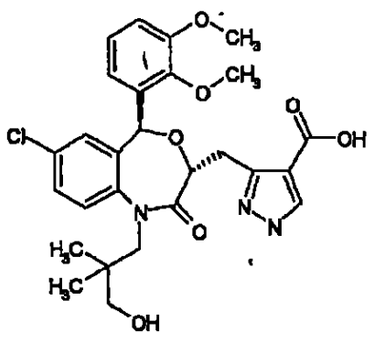
(2) Una mezcla de 3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]metil}-5-metil-1,3-oxazol-4-il)propionato de metilo (0.67 g, 1.04 mmoles) obtenido en el ejemplo 38-(1), una solución acuosa 1 N de hidróxido de sodio (2.5 ml) y etanol (7 ml) se agitó a 60°C durante 30 minutos. Esta mezcla se diluyó con agua (50 ml), se acidificó y después se extrajo con acetato de etilo (50. ml) dos veces. El extracto se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio, y después se concentró bajo presión reducida para obtener ácido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-

hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-5-metil-1,3-oxazol-4-il)propiónico (0.47 g, 0.801 mmoles, 77%) como polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.22 (3H, s), 2.62-2.72 (4H, m), 3.12-3.19 (2H, m), 3.67-3.46 (2H, m), 3.62 (3H, s), 3.63 (1H, d, J = 12.3 Hz), 3.89 (3H, s), 4.39-4.48 (2H, m), 6.19 (1H, s), 6.60 (1H, d, J = 2.1 Hz), 6.98-7.47 (5H, m).

EJEMPLO 39

Acido 3-[((3R,5S)-7-cloro-5-(2,3-dimetoxıfenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)metil]pirazol-4-ácido



(1) Se añadió dimetilacetal de N,N-dimetilformaldehído (0.41 ml) a una solución de 4-[((3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-

il)]-3-oxobutanoato de etilo (1.5 g) obtenido en el ejemplo 26-(1) en tolueno (30 ml) y la mezcla se puso a reflujo durante la noche. Después de que la solución de reacción se concentró, se añadieron etanol (30 ml) e hidrato de hidrazina (0.14 g) al residuo y la mezcla se puso a reflujo durante 3 horas. La solución de reacción se concentró y el residuo se purificó por cromatografía en columna sobre gel de sílice para obtener 3-[((3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-acetoxi-2,2-dimetilpropy1)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)metil]pirazol-4-carboxilato de etilo (0.90 g) como un aceite café.

^{1}H-RMN (CD_3OD) δ: 0.95 (3H, s), 1.02 (3H, s), 1.26 (3H, t, J = 7.4 Hz), 2.03 (3H, s), 3.47-3.55 (2H, m), 3.62 (3H, s), 3.71-3.88 (2H, m), 3.89 (3H, s), 4.08-4.15 (2H, m), 4.21 (2H, q, J = 7.4 Hz), 4.54 (1H, d, J = 14.1 Hz), 6.27 (1H, s), 6.61 (1H, s), 6.96-6.99 (1H, m), 7.10-7.33 (4H, m), 7.87 (1H, s).

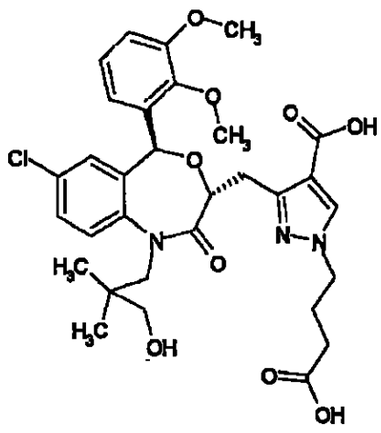
(2) Una mezcla de 3-[((3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenıl)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)]metil]pirazol-4-carboxilato de etilo (1.0 g) obtenido en el ejemplo 39-(1), una solución acuosa saturada 2 N de hidróxido de sodio (3.3 ml) y etanol (20 ml) se agitó a 80°C durante la noche. Esta mezcla se diluyó con agua (50 ml), se acidificó y después se extrajo

dos veces con cloroformo (50 ml). Este extracto se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener ácido 3-[((3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)metil]pirazol-4-carboxílico (0.18 g) como un cristal blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.06 (3H, s), 3.18 (1H, d, J = 11.7 Hz), 3.37 (1H, d, J = 15.0 Hz), 3.56-3.61 (3H, m), 3.63 (3H, s), 3.89 (3H, s), 4.14 (1H, t, J = 6.9 Hz), 4.49 (1H, d, J = 14.4 Hz), 6.19 (1H, s), 6.60 (1H, d, J = 2.4 Hz), 6.97-7.00 (1H, m), 7.08-7.10 (1H, m), 7.16-7.36 (5H, m), 7.94 (1H, s).

EJEMPLO 40

Acido 1-(3-carboxıpropil)-3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahıdro-4,1-benzoxazepin-3-il]metil}-1H-pirazol-4-carboxílico



(1) Se añadió carbonato de potasio (0.741 g) a una solución de 5-{[(3R,5S)-1-(3-(acetoxi)-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1H-pirazol-4-carboxilato de etilo (3.00 g) obtenıdo en el ejemplo 39-(1) y 4-bromobutanoato de etilo (0.794 ml) en DMF (30 ml) y la mezcla se agitó durante la noche. La solución de reacción se diluyó con acetato de etilo, se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El resıduo se purificó por cromatografía en columna sobre gel de sílice para obtener 3-{[(3R,5S)-1-(3-(acetoxi)-2,2-dimetilpropil)-7-

cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1-(4-etoxi-4-oxobutil)-1H-pirazol-4-carboxilato de etilo (0.98 g) de una primera fracción diluida y 5-({(3R,5S)-1-[3-(acetoxi)-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il}metil)-1-(4-etoxi-4-oxobutil)-1H-pirazol-4-carboxilato de etilo (1.78 g) de una segunda fracción diluida.

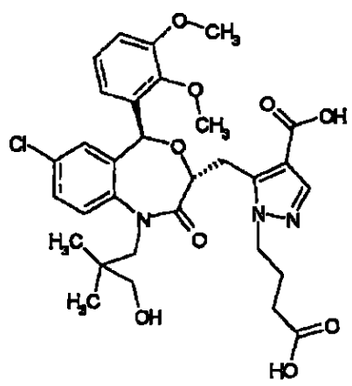
(2) A una solución de 3-{[(3R,5S)-1-(3-(acetoxi)-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1-(4-etoxi-4-oxobutil)-1H-pirazol-4-carboxilato de etilo (0.8 g) obtenido en el ejemplo 40-(1) en etanol (8 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (4 ml) y la mezcla se agitó durante la noche. La solución de reacción se neutralizó con ácido clorhídrico 1 N y se extrajo con acetato de etilo. Este extracto se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener el compuesto del título (157 mg).

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.03 (3H, s), 2.10-2.21 (2H, m), 2.28-2.38 (2H, m), 3.16 (1H, d, J = 12.1 Hz), 3.28-3.45 (2H, m), 3.52-3.69 (5H, m), 3.86 (3H, s), 4.13 (2H,

t, J = 6.22 Hz), 4.41-4.52 (2H, m), 6.17 (1H, s), 6.56 (1H, d, J = 2.07 Hz), 6.94 (1H, dd, J = 1.9, 7.9 Hz), 7.05-7.17 (2H, m), 7.30-7.40 (2H, m), 7.85 (1H, s) .

EJEMPLO 41

Acido 1-(3-carboxipropil)-5-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1H-pirazol-4-carboxílico



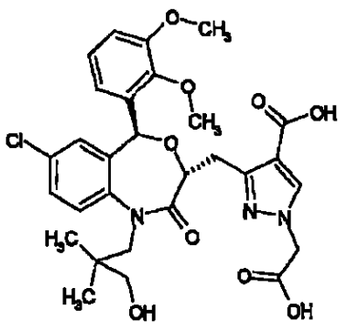
Una solución acuosa 1 N de hidróxido de sodio (4 ml) se añadió a una solución de 5-({(3R,5S)-1-[3-(acetiloxi)-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il}metil)-1-(4-etoxi-4-oxobutil)-1H-pirazol-4-carboxilato de etilo (0.75 g) obtenido en el ejemplo 40-(1) en etanol (20 ml) y la mezcla se agitó durante 2 días. La solución de reacción se neutralizó con ácido clorhídrico 1 N y se extrajo con acetato de etilo. Este extracto se lavó con una solución acuosa saturada de cloruro

de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener el compuesto del título (590 mg).

^{1}H-RMN ($CDCl_3$) δ: 0.76 (3H, s), 0.87 (3H, s), 1.83-1.96 (2H, m), 2.14 (2H, t, J = 7.3 Hz), 3.03-3.20 (2H, m), 3.23-3.43 (2H, m), 3.50 (3H, s), 3.68 (1H, d, J = 14.1 Hz), 3.83 (3H, s), 4.07-4.25 (3H, m), 4.35 (1H, d, J= 14.1 Hz), -4.57 (1H, s), 6.10 (1H, s), 6.26 (1H, d, J = 2.6 Hz), 6.59 (1H, d, J = 3.3, 5.9 Hz), 7.09-7.18 (2H, m), 7.50 (1H, dd, J = 2.5, 8.7 Hz), 7.70 (1H, d, J = 8.9Hz), 7.77 (1H, s).

EJEMPLO 42

Acido 1-(carboximetil)-3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1H-pirazol-4-carboxílico



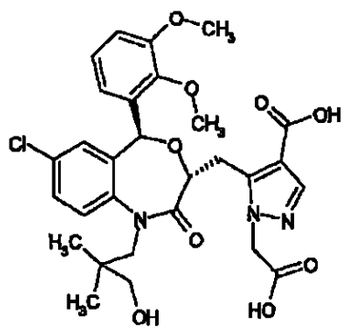
De conformidad con una manera similar a la del

ejemplo 40, se obtuvo el compuesto del título.

^{1}H-RMN (DMSO-d_6) δ: 0.76 (3H, s), 0.84 (3H, s), 3.00-3.21 (2H, m), 3.22-3.57 (5H, m), 3.65 (1H, d, J = 14.0 Hz), 3.82 (3H, s), 4.23-4.40 (2H, m), 4.50 (2H, s), 6.06 (1H, s), 6.31 (1H, d, J = 2.5 Hz), 6.96 (1H, d, J = 7.0 Hz), 7.05-7.22 (2H, m), 7.49 (1H, dd, J = 2.1, 8.7 Hz), 7.68 (1H, d, J = 8.9 Hz), 7.99 (1H, s).

EJEMPLO 43

Acido 1-(carboximetil)-5-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1H-pirazol-4-carboxílico



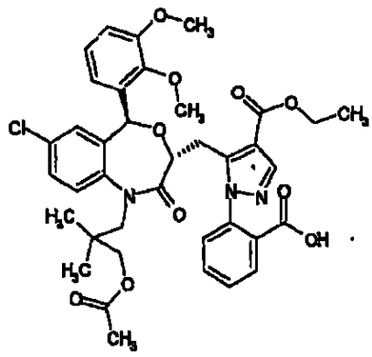
De conformidad con una manera similar a la del ejemplo 41, se obtuvo el compuesto del título.

^{1}H-RMN (DMSO-d_6) δ: 0.75 (3H, s), 0.87 (3H, s), 3.03-3.20 (2H, m), 3.24-3.41 (2H, m), 3.51 (3H, s), 3.66 (1H, d, J = 14.1 Hz), 3.84 (3H, s), 4.10-4.18 (1H, m), 4.33 (1H,

d, 10 J = 14.1 Hz), 4.51-4.60 (1H, m), 5.00 (2H, s), 6.11 (1H, s), 6.28 (1H, d, J = 2.6 Hz), 6.72 (1H, dd, J = 2.0,7.3 Hz), 7.11-7.22 (2H, m), 7.50 (1H, dd, J = 2.5, 8.7 Hz), 7.69 (1H, d, J=8.9Hz), 7.77 (1H, s).

EJEMPLO 44

Acido 2-[5-({(3R,5S)-1-[3-(acetiloxi)-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il}metil)-4-(etoxicarbonil)-1H-pirazol-1-il]benzoico



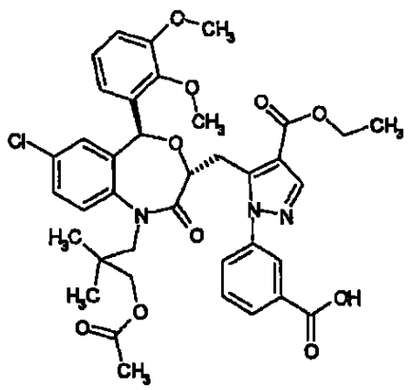
1,1-Dimetoxi-N,N-dimetilmetanamina (0.598 ml) se añadió a una solución de 4-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-3-oxobutanoato de etilo (2 g) en tolueno (20 ml) y la mezcla se puso a reflujo durante la noche. Después de que la mezcla se concentró bajo presión reducida, se añadieron etanol (20 ml) y ácido 2-hidrazinobenzoico (0.567 g) al residuo y la mezcla se puso a

reflujo durante 3 horas. Después de concentrarse bajo presión reducida, el residuo se purificó por cromatografía en columna sobre gel de sílice para obtener el compuesto del título (0.83 g).

^{1}H-RMN (DMSO-d_6) δ: 0.83-0.87 (6H, m), 1.11 (3H, t, J = 7.1 Hz), 1.89 (3H, s), 3.18-3.31 (2H, m), 3.45 (3H, s), 3.56-3.71 (3H, m), 3.83 (3H, s), 3.99-4.16 (3H, m), 4.26 (1H, d, J = 14.3 Hz), 6.00 (1H, s), 6.25 (1H, d, J = 2.3 Hz), 6.67 (1H, dd, J = 1.4, 7.3 Hz), 7.09-7.21 (2H, m), 7.38-7.45 (1H, m), 7.46-7.64 (4H, m), 7.83 (1H, d, J = 8.1 Hz), 7.97 (1H, s).

EJEMPLO 45

Acido 3-(5-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-4-(etoxicarbonil)-1H-pirazol-1-il)benzoico



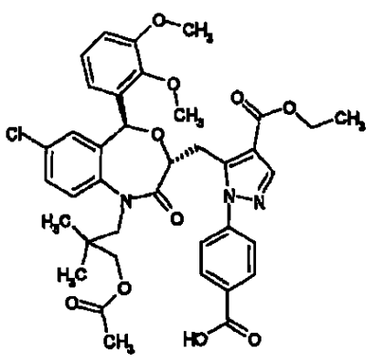
De conformidad con una manera similar a la del

ejemplo 44, se obtuvo el compuesto del título.

^{1}H-RMN (DMSO-d_6) δ: 0.85 (3H, s), 0.87 (3H, s), 1.04-1.11 (3H, m), 1.87 (3H, s), 3.28-3.38 (1H, m), 3.45 (3H, s), 3.46-3.75 (4H, m), 3.82 (3H, s), 4.10 (3H, m), 4.32 (1H, d, J = 14.3 Hz), 6.01 (1H, s), 6.20 (1H, d, J = 2.5 Hz), 6.46 (1H, dd, J = 2.6, 6.6 Hz), 7.07-7.15 (2H, m), 7.47-7.59 (2H, m), 7.68 (1H, d, J = 8.9 Hz), 7.73-7.79 (1H, m), 7.93-7.98 (1H, m), 8.02 (1H, t, J= 1.8 Hz), 8.10 (1H, s).

EJEMPLO 46

Acido 4-(5-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-4-(etoxicarbonil)-1H-pirazol-1-il)benzoico



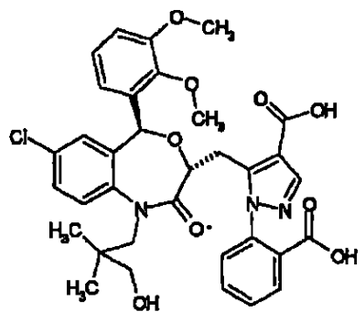
De conformidad con una manera similar a la del ejemplo 44, se obtuvo el compuesto del título.

^{1}H-RMN (DMSO-d_6) δ: 0.86 (s, 6H), 1.10 (3H, t, J = 7.1 Hz), 1.87 (3H, s), 3.38 (1H, d, J = 4.0 Hz), 3.44 (3H,

s), 3.53-3.74 (4H, m), 3.82 (3H, s), 4.03-4.15 (3H, m), 4.32 (1H, d, J = 14.3 Hz), 5.99 (1H, s), 6.22 (1H, d, J = 2.5 Hz), 6.46 (1H, dd, J = 2.1, 7.0 Hz), 7.09-7.19 (2H, m), 7.46 (1H, dd, J = 8.7, 2.5 Hz), 7.58-7.69 (3H, m), 7.94 (2H, d, J = 8.5 Hz), 8.11 (1H, s).

EJEMPLO 47

Acido 1-(2-carboxifenil)-5-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1H-pirazol-4-carboxílico



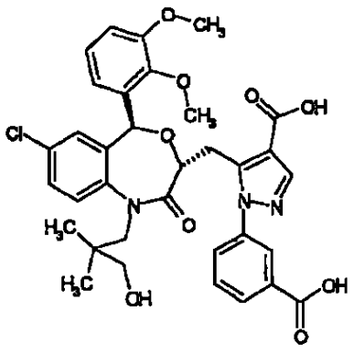
Una solución acuosa 1 N de hidróxido de sodio (3.4 ml) se añadió a una solución de ácido 2-(5-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-4-(etoxicarbonil)-1H-pirazol-1-il)benzoico (0.5 g) obtenido en el ejemplo 44 en etanol (5 ml) y la mezcla se agitó durante la noche. La solución de reacción se neutralizó con ácido clorhídrico 1 N y se extrajo con acetato de etilo. Este

extracto se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener el compuesto del título (0.28 g).

^{1}H-RMN (DMSO-d_6) δ: 0.70 (3H, s), 0.79 (3H, s), 2.96-3.12 (2H, m), 3.22-3.37 (2H, m), 3.46 (3H, s), 3.56 (1H, d, J = 14.0 Hz), 3.83 (3H, s), 4.21 (1H, d, J = 14.0 Hz), 4.50 (1H, t, J = 5.2 Hz), 5.95 (1H, s), 6.24 (1H, d, J = 2.5 Hz), 6.69 (1H, dd, J = 1.6, 7.4 Hz), 7.08-7.23 (2H, m), 7.36-7.42 (1H, m), 7.44-7.58 (4H, m), 7.76-7.85 (1H, m), 7.91 (1H, s).

EJEMPLO 48

Acido 1-(3-carboxifenil)-5-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1H-pirazol-4-carboxílico



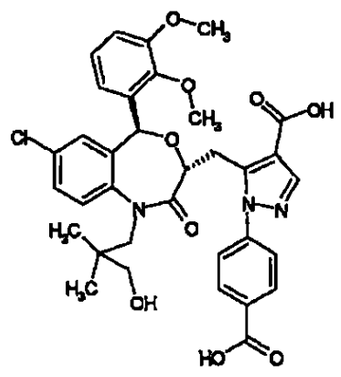
De conformidad con una manera similar a la del

ejemplo 47, se obtuvo el compuesto del título.

^{1}H-RMN (DMSO-d_6) δ: 0.70 (3H, s), 0.81 (3H, s), 2.98-3.14 (2H, m), 3.46 (3H, s), 3.48-3.66 (2H, m), 3.82 (3H, s), 4.20 (1H, dd, J = 3.9, 9.6 Hz), 4.28 (1H, d, J = 14.1 Hz), 5.96 (1H, s), 6.19 (1H, d, J = 2.5 Hz), 6.46 (1H, dd, J = 2.5, 6.7 Hz), 7.10 (2H, m), 7.43-7.65 (4H, m), 7.71-7.78 (1H, m), 7.94 (1H, d, J = 7.9 Hz), 8.02-8.06 (2H, m).

EJEMPLO 49

Acido 1-(4-carboxifenil)-5-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1H-pirazol-4-carboxílico



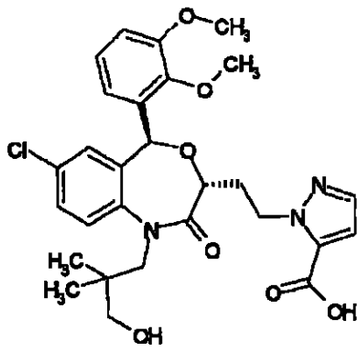
De conformidad con una manera similar a la del ejemplo 47, se obtuvo el compuesto del título.

^{1}H-RMN (DMSO-d_6) δ: 0.70 (3H, s), 0.80 (3H, s), 2.97-3.13 (2H, m), 3.45 (3H, s), 3.56-3.70 (2H, m), 3.82 (3H,

s), 4.07 (1H, dd, J = 3.9, 9.8 Hz), 4.23-4.32 (1H, m), 4.51 (1H, t, J = 4.9 Hz), 5.93 (1H, s), 6.20 (1H, d, J = 2.5 Hz), 6.47 (1H, dd, J = 1.8, 7.1 Hz), 7.07-7.20 (2H, m), 7.41 (1H, dd, J = 2.5,8.7 Hz), 7.54-7.64 (3H, m), 7.92 (2H, d, J = 8.7 Hz), 8.06 (1H, s).

EJEMPLO 50

Acido 1-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-pirazol-5-carboxílico



(1) Acido [(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acético (10 g, 19.2 mmoles) se disolvió en THF (80 ml), y se añadieron gota a gota N-metilmorfolina (2.2 ml, 23.1 mmoles) y clorocarbonato de etilo (2.54 ml, 23.1 mmoles) bajo enfriamiento con hielo al mismo. Después de agitarse a la misma temperatura durante 1 hora, la mezcla se enfrió a -30°C y se añadió borhidruro de sodio (2.18 g, 58.0

mmoles) a la misma. Posteriormente se añadió gota a gota MeOH (80 ml) en forma gradual y la mezcla se agitó durante 1 hora. A la misma temperatura, se añadió una solución acuosa saturada de cloruro de amonio a la misma y la mezcla se extrajo con AcOEt (480 ml). La capa orgánica se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro, y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (2:3)] para obtener (3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-etanol (9.3 g) como un cristal incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.03 (3H, s), 2.03 (3H, s), 2.05-2.30 (2H, m), 3.57 (1H, d, J = 13.8 Hz), 3.63 (3H, s), 3.70-3.93 (7H, m), 4.10 (1H, t, J = 6.2 Hz), 4.55 (1H, d, J = 13.8 Hz), 6.28 (1H, s), 6.64 (1H, d, J = 2.2 Hz), 6.93-7.05 (1H, m), 7.15-7.23 (2H, m), 7.31 (1H, s), 7.31 (1H, dd, J = 2.2, 8.8 Hz).

2) Bajo atmósfera de nitrógeno, se añadieron n-tributilfosfina (0.74 ml, 2.96 mmoles) y 1,1'-azodicarbonilodipiperidina (0.75 g, 2.96 mmoles) a una solución de (3R,5S)-1-(3-acetoxil-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-

benzoxazepin-3-etanol (1.0 g, 1.98 mmoles) obtenido en el ejemplo 50-(1), 1H-pirazol-5-carboxilato de metilo (0.25 g, 1.98 mmoles) y tolueno (20 ml) y la mezcla se agitó a temperatura ambiente durante 8 horas. Después de que se añadió hexano (10 ml) a la misma, la mezcla se agitó durante 30 minutos y después se filtró para remover sustancias insolubles. El filtrtado se concentró bajo presión reducida y el residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (70:30-65:35)] para obtener 1-{2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-pirazol-5-carboxilato de metilo (0.81 g) como polvo no cristalino incoloro de una primera fracción diluida y 1-{2-[(3R,5S)-(1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-pirazol-3-carboxilato de metilo (0.17 g) como polvo incoloro de una segunda fracción diluida.

Primera fracción diluida

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.02 (3H, s), 2.02 (3H, s), 2.30-2.41 (2H, m), 3.50 (1H, d, J = 14.1 Hz), 3.60 (3H, s), 3.73 (1H, d, J = 11.4 Hz), 3.77 (1H, t, J = 6.6 Hz), 3.82 (3H, s), 3.84 (1H, d, J = 11.4 Hz), 3.88 (3H, s), 4.55 (1H, d, J = 14.1 Hz), 4.65-4.75 (2H, m), 6.24 (1H, s), 6.60

(1H, d, J = 2.4 Hz), 6.74 (1H, d, J = 2.1 Hz), 6.97 (1H, dd, J = 1.5, 8.1 Hz), 7.10-7.27 (3H, m), 7.30 (1H, dd, J = 2.4, 8.4 Hz), 7.35 (1H, d, J = 2.1 Hz).

Segunda fracción diluida

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.01 (3H, s), 2.02 (3H, s), 2.30-2.45 (2H, m), 3.50 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.71 (1H, d, J = 11.1 Hz), 3.78 (1H, t, J = 6.9 Hz), 3.84 (1H, d, J = 11.1 Hz), 3.89 (6H, s), 4.28-4.50 (2H, m), 4.51 (1H, d, J = 14.1 Hz), 6.24 (1H, s), 6.62 (1H, d, J = 2.4 Hz), 6.71 (1H, d, J = 2.4 Hz), 6.95-7.02 (1H, m), 7.18-7.22 (2H, m), 7.26 (1H, d, J = 8.7 Hz), 7.32 (1H, dd, J = 2.4, 8.7 Hz), 7.37 (1H, d, J = 2.4 Hz)

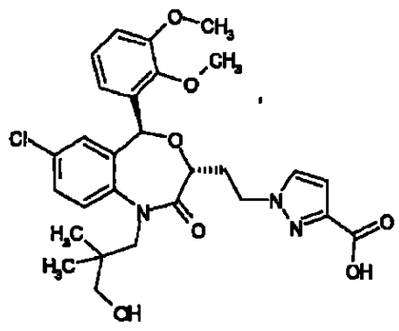
(3) Una mezcla de 1-{2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-pirazol-5-carboxilato de metilo (0.72 g, 1.17 mmoles) obtenido en el ejemplo 50-(2), una solución acuosa 1 N de hidróxido de sodio (4.0 ml) y etanol (14 ml) se agitó a temperatura ambiente durante 3 horas. Esta mezcla se acidificó con ácido clorhídrico 1 N (5.0 ml) y se añadió acetato de etilo (150 ml). La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El cristal resultante se recristalizó con acetato de etilo-

hexano para obtener ácido 1-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-pirazol-5-carboxílico (0.63 g) como un cristal incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 2.28-2.50 (2H, m), 3.16 (1H, d, J = 12.3 Hz), 3.35 (1H, d, J = 14.4 Hz), 3.60 (3H, s), 3.62 (1H, d, J = 12.3 Hz), 3.79 (1H, t, J = 6.6 Hz), 3.88 (3H, s), 4.43 (1H, d, J = 14.4 Hz), 4.59-4.81 (2H, m), 6.12 (1H, s), 6.58 (1H, d, J=2.1Hz), 6.84 (1H, d, J = 2.1 Hz), 6.97 (1H, dd, J = 1.5, 7. 8 Hz), 7.20 (1H, t, J = 7.8 Hz), 7.21-7.29 (2H, m), 7.32 (1H, dd, J = 2.1, 8.7 Hz), 7.40 (1H, d, J = 2.1 Hz).

EJEMPLO 51

Acido 1-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-pirazol-3-carboxílico



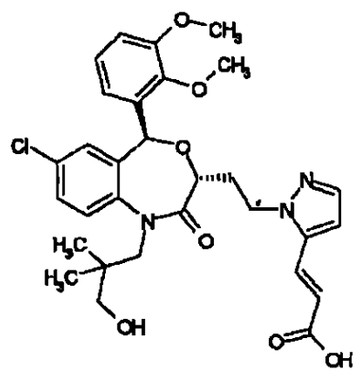
Una mezcla de 1-{2-[(3R,5S)-1-(3-acetoxi-2,2-

dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-pirazol-3-carboxilato de metilo (0.17 g, 0.28 mmoles) obtenido en el ejemplo 50-(2), una solución acuosa 1 N de hidróxido de sodio (1.0 ml) y etanol (5 ml) se agitó a temperatura ambiente durante 3 horas. Posteriormente, se añadió una solución acuosa 1 N de hidróxido de sodio (1.5 ml) y la mezcla se agitó durante 3 horas. Esta mezcla se acidificó con ácido clorhídrico 1 N (2.8 ml)y después se añadió acetato de etilo (80 ml). La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El cristal resultante se recristalizó con acetato de etilo-hexano para obtener ácido 1-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-pirazol-3-carboxílico (0.12 g) como un cristal incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.63 (3H, s), 1.05 (3H, s), 2.30-2.50 (2H, m), 3.15 (1H, d, J = 11.1 Hz), 3.36 (1H, d, J = 14.4 Hz), 3.60 (1H, d, J = 11.1 Hz), 3.61 (3H, s), 3.82 (1H, t, J = 6.6 Hz), 3.90 (3H, s), 4.30-4.50 (3H, m), 6.15 (1H, s), 6.61 (1H, s), 6.75-6.87 (1H, m), 7.15-7.50 (5H, m).

EJEMPLO 52

Acido (2E)-3-(1-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)etil]-1H-pirazol-5-il}acrílico

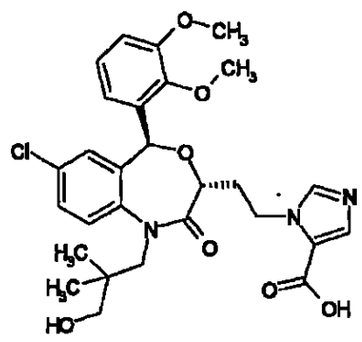


De conformidad con una manera similar a la del ejemplo 19, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 1.26 (3H, t, J = 7.0 Hz), 2.29-2.45 (2H, m), 3.15 (1H, d, J = 11.8 Hz), 3.36 (1H, d, J = 14.2 Hz), 3.64 (1H, d, J = 11.8 Hz), 3.36 (1H, d, J = 14.2 Hz), 3.64 (1H, d, J = 11.8 Hz), 3.65 (3H, s), 3.85 (1H, t, J = 6.2 Hz), 3.90 (3H, s), 4.21-4.40 (2H, m), 4.44 (1H, d, J= 14.2 Hz), 6.15 (1H, s), 6.32 (1H, d, J: 16.0 Hz), 6.41 (1H, d, J = 2.2 Hz), 6.60 (1H, d, J = 1.8 Hz), 6.95-7.10 (1H, m), 7.16-7.30 (2H, m), 7.26-7.41 (3H, m), 7.64 (1H, d, J= 16.0 Hz).

EJEMPLO 53

Acido 1-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-imidazol-5-carboxílico

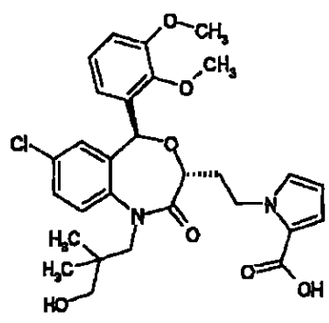


De conformidad con una manera similar a la del ejemplo 50, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 2.29-2.40 (2H, m), 3.15 (1H, d, J = 12.0 Hz), 3.36 (1H, d, J = 14.1Hz), 3.60 (1H, d, J= 12.0 Hz), 3.61 (3H, s), 3.85 (1H, t, J = 7.5 Hz), 3.89 (3H, s), 4.44 (1H, d, J = 14.1 Hz), 6.14 (1H, s), 6.61 (1H, d, J= 2.1 Hz), 6.98-7.02 (1H, m), 7.13-7.26 (2H, m), 7.28 (1H, d, J = 8.7 Hz), 7.34 (1H, dd, J = 2.1, 8.7 Hz), 7.64 (1H, s), 7.77 (1H, s).

EJEMPLO 54

Acido 1-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-pirrol-2-carboxílico

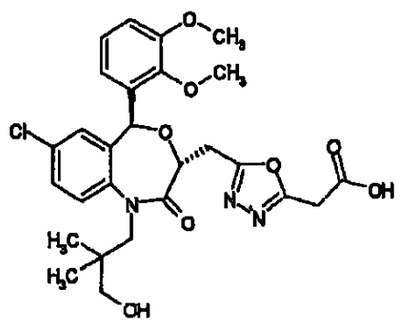


De conformidad con una manera similar a la del ejemplo 50, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 2.21-2.39 (2H, m), 3.14 (1H, d, J = 11.4 Hz), 3.35 (1H, d, J = 14.4 Hz), 3.61 (1H, d, J = 11.4 Hz), 3.61 (3H, s), 3.75 (1H, t, J = 6.9 Hz), 3.89 (3H, s), 4.30-4.61 (2H, m), 4.44 (1H, d, J = 14.4 Hz), 6.05-6.10 (1H, m), 6.13 (1H, s), 6.60 (1H, d, J = 2.1 Hz), 6.81-6.90 (1H, m), 6.94-7.03 (2H, m), 7.15-7.30 (3H, m), 7.32 (1H, dd, J = 2.1, 8.7 Hz).

EJEMPLO 55

Acido (5-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3,4-oxadiazol-2-il)acético



(1) Se añadió cloruro de pivaloilo (2.8 ml) a una solución de ácido 2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil}-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il] acético (10 g) y trietilamina (3.2 ml) en THF (100 ml) a 0°C y la mezcla se agitó a 0°C durante 30 minutos. A la solución de reacción a 0°C, se añadió 3-hydrazino-3-oxopropionato de etilo (3.5 g) y después se añadió gota a gota trietilamina (3.2 ml). La mezcla se agitó a temperatura ambiente durante 2 horas y la solución de reacción se diluyó con acetato de etilo (50 ml). Este extracto se lavó con ácido clorhídrico 0.1 N, una solución acuosa al 5% de sulfato ácido de potasio, una solución acuosa de bicarbonato de sodio y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se

purificó por cromatografía en columna sobre gel de sílice para obtener 3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}hydrazino)-3-oxopropionato de etilo (2.5 g) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.00 (3H, s), 1.25 (3H, t, J = 7.2 Hz), 2.02 (3H, s), 2.70-2.77 (1H, m), 2.92-3.00 (1H, m), 3.39 (2H, s), 3.53 (1H, d, J = 14.2 Hz), 3.60 (3H, s), 3.69-3.87 (2H, m), 3.88 (3H, s), 4.19 (2H, q, J = 7.2 Hz), 4.22-4.39 (1H, m), 4.54 (1H, d, J = 14.4 Hz), 6.25 (1H, s), 6.63 (1H, d, J = 1.8 Hz), 6.96-6.99 (1H, s), 7.15-7.24 (2H, m), 7.28-7.35(2H, m).

(2) Se añadió oxicloruro de fósforo (0.8 ml) a una solución de 3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}hidrazino)-3-oxopropionato de etilo (3.7 g) obtenido en el ejemplo 55-(1) en DMF (50 ml) y la mezcla se puso a reflujo durante la noche. La solución de reacción se concentró bajo presión reducida, se vació en una solución acuosa de carbonato de potasio, y se extrajo con acetato de etilo. Este extracto se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de

sílice para obtener 5-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxıfenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]metil}-1,3,4-oxadiazol-2-il)acetato de etilo (1.2 g) como un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 1.26 (3H, t, J = 6.9 Hz), 2.03 (3H, s), 3.31-3.57 (3H, m), 3.61 (3H, s), 3.75-3.87 (2H, m), 3.88 (3H, s), 3.91 (2H, s), 4.17 (2H, q, J = 6.9 Hz), 4.46-4.57 (2H, m), 6.30 (1H, s), 6.61 (1H, d, J = 2.1 Hz), 6.95-6.98 (1H, m), 7.05-7.19 (2H, m), 7.33- 7.34 (2H, m).

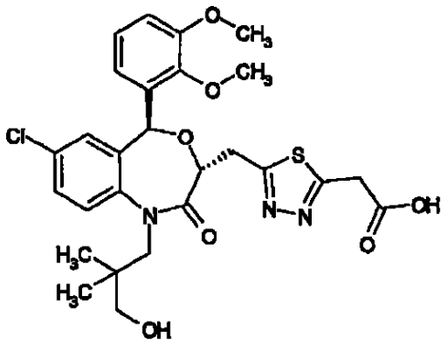
(3) Una mezcla de 5-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]metil}-1,3,4-oxadiazol-2-il)acetato de etilo (1.1 g) obtenido en el ejemplo 55-(2), una solución acuosa 1 N de hidróxido de sodio (9.35 ml) y metanol (20 ml) se agitó a temperatura ambiente durante 30 minutos. Esta mezcla se diluyó con agua (50 ml), se acidificó y se extrajo dos veces con cloroformo (50 ml). Este extracto se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener ácido (5-{[(3R,5S)-7-cloro-5-(2,3-

dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3,4-oxadiazol-2-il)acético (0.19 g) como un cristal blanco.

^{1}H-RMN (DMSO-d_6) δ: 0.63 (3H, s), 0.92 (3H, s), 3.12-3.16(2H, m), 3.38-3.44 (2H, m), 3.56 (3H, s), 3.61-3.79 (2H, m), 3.85 (3H, s), 4.24-4.50 (3H, m), 6.14 (1H, s), 6.55 (1H, s), 6.92-6.95 (1H, m), 7.12-7.17 (2H, m), 7.31-7.37(2H, m).

EJEMPLO 56

Acido (5-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3,4-tiadiazol-2-il)acético



(1) Una solución de 3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}hidrazino)-3-oxopropionato de etilo (1.09) obtenido en el ejemplo 55-(1) y reactivo de Lawesson (0.96 g) en THF (50 ml) se agitó a 80°C

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durante 1 hora. La solución de reacción se vació en agua, seguido por extracción con acetato de etilo. Este extracto se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener 2-(5-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]metil}-1,3,4-tiadiazol-2-il)acetato de etilo (0.8 g) como un cristal amorfo blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 1.30 (3H, t, J = 7.0 Hz), 2.03 (3H, s), 3.51-3.58 (1H, m), 3.62 (3H, s), 3.66-3.87 (4H, m), 3.89 (3H, s), 4.11-4.16 (2H, m), 4.24 (2H, q, J = 7.0 Hz), 4.35 (1H, t, J = 6.4 Hz), 4.55 (1H, d, J = 14.3 Hz), 6.32 (1H, s), 6.61 (1H, d, J = 1.9 Hz), 6.99 1H, dd, J = 2.3, 7.5 Hz), 7.17-7.20 (2H, m), 7.30-7.32 (2H, m).

(2) Una mezcla de 2-(5-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]metil}-1,3,4-tiadiazol-2-il)acetato de etilo (0.9 g) obtenido en el ejemplo 56-(1), una solución acuosa saturada 1 N de hidróxido de sodio (8.0 ml) y metanol (20 ml) se agitó a temperatura ambiente durante 30 minutos. Esta mezcla se diluyó con agua

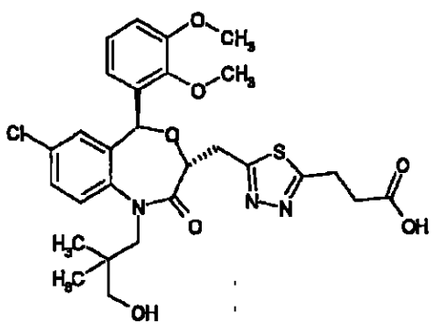
(50 ml), se acidificó y se extrajo dos veces con cloroformo (50 ml). Este extracto se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener ácido 2-(5-{[(3R,5S)-1-(3-hidroxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]metil}-1,3,4-tiadiazol-2-il)acético (0.19 g) como un cristal blanco.

^{1}H-RMN (DMSO-d_6) δ: 0.76 (3H, s), 0.84 (3H, s), 3.06-3.18 (2H, m), 3.35-3.49 (2H, m), 3.52 (3H, s), 3.66-3.71 (1H, m), 3.78 (2H, s), 3.84 (3H, s), 4.26-4.35 (2H, m), 6.14 (1H, s), 6.38 (1H, d, J = 2.3 Hz), 7.06-7.22 {3H, m), 7.51-7.55 (1H, m), 7.71(1H, d, J = 9.0 Hz).

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EJEMPLO 57

Acido 3-(5-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxil-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3,4-tiadiazol-2-il)propiónico



(1) Se añadió cloruro de pivaloilo (2.8 ml) a una solución de ácido 2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3, 5-tetrahidro-4,1-benzoxazepin-3-il]acético (10 g) y trietilamina (3.2 ml) en THF (100 ml) a 0°C y la mezcla se agitó a 0°C durante 30 minutos a la solución de reacción a 0°C, se añadió 4-hidrazino-4-oxobutanoato de etilo (3.7 g) y después se añadió gota a gota trietilamina (3.2 ml). Después de agitarse a temperatura ambiente durante 2 horas, la solución de reacción se diluyó con acetato de etilo (50 ml). Esta solución diluida se lavó con ácido clorhídrico 0.1 N, una solución acuosa al 5% de sulfato ácido de potasio, una solución acuosa de bicarbonato de sodio y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se

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purificó por cromatografía en columna sobre gel de sílice para obtener 4-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]acetil)hidrazino)-4-oxobutanoato de etilo (3.6 g) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.00 (3H, s), 1.25 (3H, t, J = 7.2 Hz), 2.03 (3H, s), 2.54 (3H, t, J = 6.4 Hz), 2.66-2.75 (3H, m), 2.89-2.97 (1H, m), 3..54 (1H, d, J = 14.3 Hz), 3.61 (3H, s), 3.69-3.88 (2H, m), 3.89 (3H, s), 4.15 (2H, q, J = 7.2 Hz), 4.33-4.38 (1H, m), 4.54 (1H, d, J = 13.9 Hz), 6.26 (1H, s), 6.64 (1H, d, J = 1.9 Hz), 6.97-7.00 (1H, s), 7.16-7.23 (2H, m), 7.32-7.36(2H, m), 8.11 (1H, brd), 8.31 (1H, brd).

(2) Una solución de 4-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]acetil}hidrazino)-4-oxobutanoato de etilo (1.0 g) obtenido en el ejemplo 57-(1) y reactivo de Lawesson (0.92 g) en THF (50 ml) se agitó a 80°C durante 1 hora. La solución de reacción se vació en agua y después se extrajo con acetato de etilo. Este extracto se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener 3-(5-{[(3R,5S)-1-(3-

acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]illetil}-1,3,4-tiadiazol-2-il)propionato de etilo (0.7 g) como polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 1.29 (3H, t, J = 7.2 Hz), 2.03 (3H, s), 2.85 (2H, t, J = 7.4 Hz), 3.37 (3H, t, J = 7.4 Hz), 3.48-3.55 (2H, m), 3.62 (3H, s), 3.65-3.87 (2H, m), 3.90 (3H, s), 4.15 (2H, q, J = 7.2 Hz), 4.35 (1H, t, J = 6.4 Hz), 4.54 (1H, d, J = 14.3 Hz), 6.31 (1H, s), 6.61 (1H, d, J = 2.3 Hz), 6.98-7.01 (1H, m), 7.13-7.23 (2H, m), 7.28-7.35(2H, m).

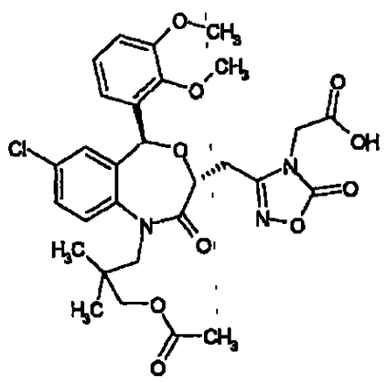
(3) Una mezcla de 3-(5-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3,4-tiadiazol-2-il)propionato de etilo (0.7 g) obtenido en el ejemplo 57-(2), una solución acuosa 1 N de hidróxido de sodio (8.0 ml) y metanol (20 ml) se agitó a temperatura ambiente durante 30 minutos. Esta mezcla se diluyó con agua (50 ml), se acidificó y se extrajo dos veces con cloroformo (50 ml). Este extracto se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener ácido 3-(5-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxil-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-

benzoxazepin-3-il]metil}-1,3,4-tiadiazol-2-il)propiónico (0.19 g) como un cristal blanco.

^{1}H-RMN (DMSO-d_6) δ: 0.78 (3H, s), 0.88 (3H, s), 2.75 (3H, t, J = 7.0 Hz), 3.08-3.20 (2H, m) 3.26 (3H, t, J = 7.0 Hz), 3.49-3.52 (1H, m), 3.53 (3H, s), 3.67-3.81 (1H, m), 3.85 (3H, s), 4.27-4.37 (2H, m) 4.58 (1H, brs), 6.16 (1H, s), 6.40 (1H, d, J = 2.6 Hz), 7.02-7.05 (1H, m), 7.14-7.26 (2H, m), 7.54 (1H, dd, J = 2.6, 8.7 Hz), 7.72(1H, d, J = 8.7 Hz).

EJEMPLO 58

Acido {3-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-5-oxo-1,2,4-oxadiazol-4(5H)-il)acético



(1) Trietilamina (10.0 ml, 0.0717 mol) se añadió a una suspensión de clorhidrato de hidroxilamina (4.98 g, 0.0717 mol) en DMSO y la mezcla se agitó durante 30 minutos.

La solución de reacción se filtró y al filtrado se añadió acetato de 3-[(3R,5S)-7-cloro-3-(cianometil)-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (7.18 g, 0.0143 moles). La mezcla se agitó a 80°C durante 18 horas. La solución de reacción se extrajo con acetato de etilo, se lavó sucesivamente con una solución acuosa 1 N de hidróxido de sodio y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener acetato de 3-[(3R,5S)-3-[(2Z)-2-amino-2-(hidroxiimino)etil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (7.9 g) como una acetona que contiene una sustancia amorfa.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.02 (3H, s), 2.03 (3H, s), 2.59 (1H, dd, J = 6.1, 14.4 Hz), 2.72-2.80 (1H, m), 3.50-3.66 (4H, m), 3.72 (1H, d, J = 11.0 Hz), 3.82-3.88 (1H, m), 3.89 (3H, s), 4.05-4.16 (1H, m), 4.54 (1H, d, J = 14.2 Hz), 4.94 (2H, s), 6.25 (1H, s), 6.62 (1H, d, J = 2.2 Hz), 6.95-7.01 (1H, m), 7.15-7.23 (2H, m), 7.28-7.35 (2H, m).

(2) CDI (1.34 g, 8.24 mmoles) y DBU (1.23 ml, 8.24 mmoles) se añadieron a una solución de acetato de 3-[(3R,5S)-3-[(2Z)-2-amino-2-(hidroxiimino)etil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (4.0 g, 7.49 mmoles) obtenido en el

ejemplo 58-(1) en THF (40 ml) y la mezcla se agitó a temperatura ambiente durante 20 horas. La solución de reacción se extrajo con acetato de etilo, se lavó sucesivamente con una solución acuosa 1 N de ácido clorhídrico y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (3:2-2:3)] para obtener acetato de 3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-3-[(5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-il)metil]-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (2.53 g) como una sustancia amorfa incolora.

^{1}H-RMN ($CDCl_3$) δ: 0.97 (3H, s), 1.00 (3H, s), 2.05 (3H, 25 s), 3.01 (1H, dd, J = 4.0, 15.0 Hz), 3.11 (1H, dd, J = 6.9, 15.0 Hz), 3.53 (1H, d, J = 14.2 Hz), 3.65 (3H, s), 3.68 (1H, d, J = 11.2 Hz), 3.89 (3H, s), 3.95 (1H, d, J = 11.2 Hz), 4.20 (1H, dd, J = 4.2 I 6.8 Hz), 4.58 (1H, d, J = 14.2 Hz), 6.24 (1H, s), 6.67 (1H, d, J = 2.4 Hz), 7.00 (1H, dd, J = 5 1.7,8.1 Hz), 7.10-7.22 (2H, m), 7.29-7.40 (2H, m).

(3) Se añadió hidruro de sodio (46 mg, 1.16 mmoles) a una solución de acetato de 3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-3-[(5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-il)metil]-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-

dimetilpropilo (0.6 g, 0.893 mmoles) obtenido en el ejemplo 58-(2) en DMF bajo enfriamiento con hielo y la mezcla se agitó durante 30 minutos. A la solución de reacción se añadió bromoacetato de t-butilo y la mezcla se agitó durante 1.5 horas bajo enfriamiento con hielo y después a temperatura ambiente durante 30 minutos. Después de que se añadió ácido clorhídrico 1 N a la solución de reacción, la mezcla se extrajo con acetato de etilo, se lavó sucesivamente agua y una solución acuosa saturada de cloruro de sodio, y después se secó sobre sulfato de magnesio. Después de concentrarse bajo presión reducida, el residuo se purificó por cromatografía en columna sobre gel de sílice (solvente de revelado: hexano-acetato de etilo (3:1-2:1)) para obtener (3-{[(3R,5S)-1-(3-acetoxi)-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il}metil)-5-oxo-1,2,4-oxadiazol-4(5H)-ilacetato de ter-butilo (0.43 g).

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.01 (3H, s), 1.47 (9H, s), 2.03 (3H, s), 2.94-3.09 (2H, m), 3.55 (1H, d, J = 14.2 Hz), 3.61 (3H, s), 3.71 (1H, d, J = 11.2 Hz), 3.85 (1H, d, J = 11.0 Hz), 3.89 (3H, s), 4.34-4.39 (3H, m), 4.51 (1H, d, J = 14.2Hz), 6.28 (1H, s), 6.63 (1H, d, J = 2.2Hz), 6.97-7.06 (2H, m), 7.19 (1H, t, J = 7.9 Hz), 7.29-7.39 (2H, m).

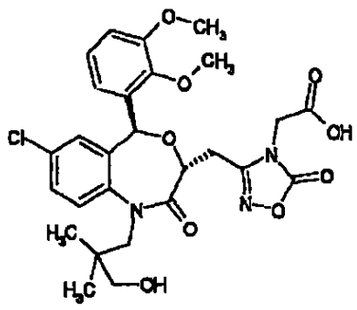
(4) Se añadió ácido trifluoroacético (5 ml) a (3-

{[(3R,5S)-1-(3-acetiloxi)-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il}metil)-5-oxo-1,2,4-oxadiazol-4(5H)-ilacetato de ter-butilo (0.42 g, 0.616 mmoles) obtenido en el ejemplo 58-(3) bajo enfriamiento con hielo y la mezcla se agitó durante 30 minutos y después a temperatura ambiente durante 50 minutos. La solución de reacción se concentró bajo presión reducida para obtener ácido [3-{[(3R,5S)-1-(3-acetiloxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-5-oxo-1,2,4-oxadiazol-4(5H)-il]acético (0.40 g).

^{1}H-RMN ($CDCl_3$) δ: 0.96 (3H, s), 0.98 (3H, s), 2.05 (3H, 20 s), 3.05-3.08 (2H, m), 3.54 (1H, d, J = 14.2 Hz), 3.62 (3H, s), 3.73 (1H, d, J = 11.0 Hz), 3.85-3.95 (4H, m), 4.34 (1H, t, J = 11.0 Hz), 4.47-4.54 (3H, m), 6.27 (1H, s), 6.62 (1H, d, J=2.2Hz), 6.98-7.39 (6H, m).

EJEMPLO 59

Acido [3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxıfenil)-1-(3-hidroxi-2,2-dimetılpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-5-oxo-1,2,4-oxadiazol-4(5H)-il]acético



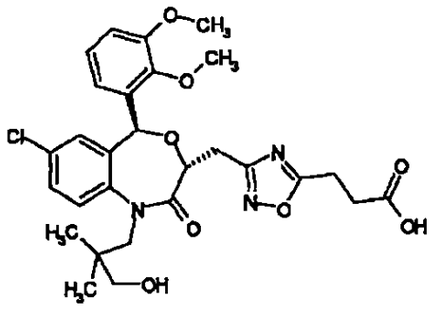
Una solución acuosa 1 N de hidróxido de sodio (1.21 ml, 1.21 mmoles) se añadió a una mezcla de ácido (3-{[(3R,5S)-1-(3-acetiloxi)-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-5-oxo-1,2,4-oxadiazol-4(5H)-il)acético (0.25 g, 0.405 mmoles) obtenido en el ejemplo 58 en etanol-THF (1:1) (3 ml) y la mezcla se agitó durante 2 horas. La solución de reacción se acidificó con ácido clorhídrico 1 N (1.5 ml), se extrajo con acetato de etilo, se lavó con agua y una solución acuosa saturada de cloruro de sodio, y después se secó sobre sulfato de magnesio. Después de concentrarse bajo presión reducida, el residuo se purificó por CLAR preparativa para obtener ácido [3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-

benzoxazepin-3-il]metil}-5-oxo-1,2,4-oxodiazol-4(5H)-il]acético (0.16 g).

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 3.09 (2H, d, J = 7.4 Hz), 3.24 (1H, d, J = 12.1 Hz), 3.42 (1H, d, J = 14.6 Hz), 3.58-3.65 (4H, m), 3.87-3.90 (4H, m), 4.34 (1H, t, J = 6.7 Hz), 4.41 (1H, d, J = 14.6 Hz), 4.46 (2H, s), 6.16 (1H, s), 6.61 (1H, d, J = 2.2Hz), 7.00 (2H, d, J = 8.3Hz), 7.16-7.43 (3H, m).

EJEMPLO 60

Acido 3-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)propiónico



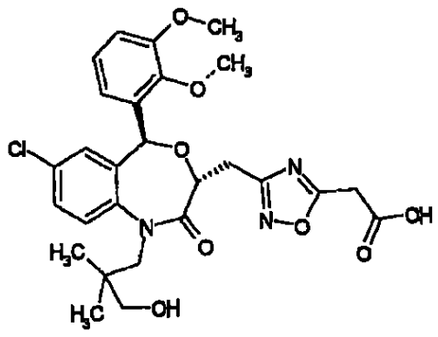
Trietilamina (0.44 ml, 3.18 mmoles) y 4-cloro-4-oxobutirato de etilo (0.29 ml, 2.06 mmoles) se añadieron gota a gota a una solución de acetato de 3-[(3R,5S)-3-[(2Z)-2-amino-2-(hidroxiimino)etil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo

(1.0 g, 1.87 mmoles) obtenido en el ejemplo 58-(1) en THF (10 ml) bajo enfriamiento con hielo y la mezcla se agitó a temperatura ambiente durante 24 horas. Después de que la solución de reacción se concentró bajo presión reducida, se añadió agua (10 ml) y la mezcla se calentó a reflujo durante 22 horas. La solución de reacción se extrajo con acetato de etilo, se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó sobre sulfato de magnesio. Después de concentrarse bajo presión reducida, el residuo se disolvió en etanol (10 ml) y una solución acuosa 2 N de hidróxido de sodio (3.74 ml, 7.48 mmoles) se añadió a la misma. La mezcla se agitó después durante 2 horas. La solución de reacción se diluyó con agua y después se extrajo con éter dietílico. El extracto se acidificó con ácido clorhídrico 6 N, se extrajo con acetato de etilo, se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. Después de que el residuo se disolvió en etanol, se añadió carbón activado al mismo y la mezcla se agitó durante 10 minutos. Las sustancias insolubles se filtraron y el filtrado se concentró bajo presión reducida para obtener ácido 3-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)propiónico (0.66 g).

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 2.89 (2H, d, J = 7.2 Hz), 3.12-3.27 (4H, m), 3.34-3.43 (2H, m), 3.58-3.67 (4H, m), 3.89 (3H, s), 4.39-4.52 (2H, m), 6.19 (1H, s), 6.60 (1H, d, J = 1.5 Hz), 6.96-7.40 (5H, m).

EJEMPLO 61

Acido 2-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)acético

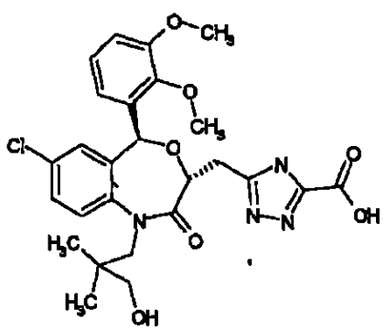


De conformidad con una manera similar a la del ejemplo 60, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 3.17-3.44 (4H, m), 3.60-3.67 (4H, m), 3.88 (3H, s), 3.99 (2H, s), 4.43-4.50 (2H, m), 6.18 (1H, s), 6.60 (1H, d, J = 1.5 Hz), 6.96-7.41 (4H, m).

EJEMPLO 62

Acıdo 3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hıdroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1H-1,2,4-triazol-5-carboxílico



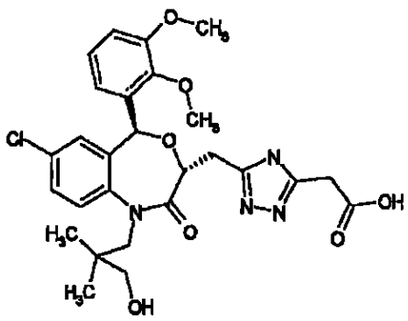
Se añadió yodometano (0.2 ml) a una solución de 3-acetato de [(3R,5S)-3-(2-amino-2-tioxoetil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (2 g) obtenido en el ejemplo 16-(2) en acetona (20 ml) y la mezcla se agitó durante la noche. Después de concentrarse bajo presión reducida, se añadieron butanol (20 ml) e hidrazino(oxo)acetato de etilo (0.317 g) al residuo y la mezcla se puso a reflujo durante 2 horas. Después de concentrarse bajo presión reducida, se añadieron etanol (20 ml) y una solución acuosa 1 N de hidróxido de sodio (4 ml) al residuo y la mezcla se agitó durante la noche. La solución de reacción se neutralizó con ácido clorhídrico 1 N y se extrajo con acetato de etilo. Este extracto se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se

concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener el compuesto del título (0.32 g).

^{1}H-RMN ($CDCl_3$) δ: 0.76 (3H, s), 0.86 (3H, s), 3.05-3.22 (3H, m), 3.51 (3H, s} , 3.67 (1H, d, J = 14.1 Hz), 3.83 (3H, s), 4.25-4.42 (2H, m), 4.56 (1H, s), 6.11 (1H, s), 6.35 (1H, d, J = 2.5Hz), 6.78 (1H, s), 7.10-7.18 (2H, m), 7.55 (1H, dd, J = 2.5,8.9 Hz), 7.72 (1H, d, J = 8.9 Hz).

EJEMPLO 63

Acido (3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1H-1,2,4-triazol-5-il)acético



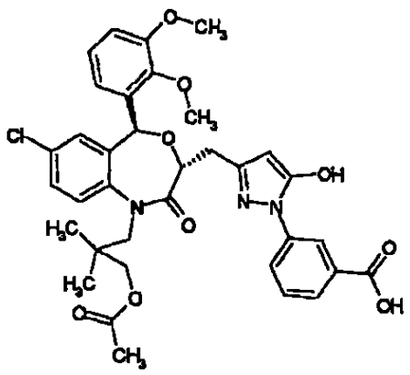
De conformidad con una manera similar a la del ejemplo 62, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.75 (3H, s), 0.86 (3H, s), 3.04-3.19 (4H, m), 3.50 (3H, s), 3.65-3.72 (3H, m), 3.83 (3H, s), 4.28-4.40 (2H, m), 6.10 (1H, s), 6.34 (1H, d, J = 2.4Hz),

6.86 (1H, dd, J = 2.3, 7.0 Hz.), 7.09-7.20 (1H, m), 7.55 (1H, dd, J = 2.4, 8.9 Hz), 7.71 (1H, d, J = 8.9 Hz).

EJEMPLO 64

Acido 3-[3-({(3R,5S)-1-[3-(acetiloxi)-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3-5-tetrahidro-4,1-benzoxazepin-3-il}metil)-5-hidroxi-1H-pirazol-1-il]benzoico



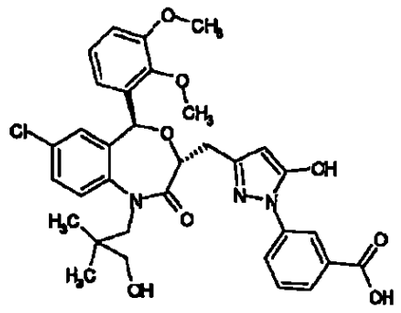
A una solución de 4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]}-3-oxobutanoato de etilo (2 g) obtenido en el ejemplo 26-(1) en etanol (20 ml), se añadió ácido 3-hidrazinobenzoico (0.567 g) y la mezcla se puso a reflujo durante la noche. Después de concentrarse bajo presión reducida, el residuo se purificó por cromatografía en columna sobre gel de sílice para obtener el compuesto del título (1.9 g).

^{1}H-RMN (DMSO-d_6) δ: 0.92 (6H, s), 1.99 (3H, s),

2.79-3.07 (2H, m), 3.52 (3H, s), 3.61-3.80 (3H, m), 3.85 (3H, s), 4.19 (1H, t, J = 6.5 Hz), 4.36 (1H, d, J = 14.3 Hz), 5.42 (1H, s), 6.13 (1H, s), 6.39 (1H, d, J=2.4Hz), 7.10-7.24 (.3H, m), 7.48-7.59 (2H, m), 7.75 (2H, t, J = 9.0 Hz), 7.95 (1H, d, J = 7.9 Hz), 8.28 (1H, s).

EJEMPLO 65

Acido 3-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-5-hidroxi-1H-pirazol-1-il)benzoico



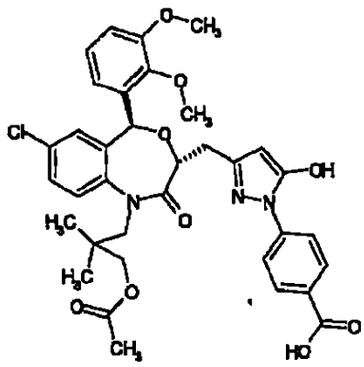
Una solución acuosa 1 N de hidróxido de sodio (3.4 ml) se añadió a una solución de ácido 3-[3-({(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3-5-tetrahidro-4,1-benzoxazepin-3-il]metil}-5-hidroxi-1H-pirazol-1-il)benzoico (0.9 g) obtenido en el ejemplo 64 en etanol (4.5 ml) y la mezcla se agitó durante la noche. La solución de reacción se neutralizó con ácido clorhídrico 1 N y se extrajo con acetato de etilo. Este extracto se lavó con una solución acuosa saturada de cloruro

de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener el compuesto del título (0.586 g).

^{1}H-RMN (DMSO-d_6) δ: 0.78 (3H, s), 0.86 (3H, s), 2.78- 3.24 (4H, m), 3.53 (3H, s), 3.69 (1H, d, J = 14.1 Hz), 3.85 (3H, s), 4.18 (1H, t, J = 6.5 Hz), 4.32 (1H, d, J = 14.1 Hz), 4.56 (1H, t, J = 4.9 Hz), 5.42 (1H, s), 6.12 (1H, s), 6.39 (1H, d, J = 2.4 Hz), 7.07-7.26 (3H, m), 7.47-7.60 (2H, m), 7.67-7.81 (2H, m), 7.95 (1H, d, J = 8.1 Hz), 8.29 (1H, s).

EJEMPLO 66

Acido 4-[3-({(3R,5S)-1-[3-(acetiloxi)-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il}metil)-5-hidroxi-1H-pirazol-1-il]benzoico



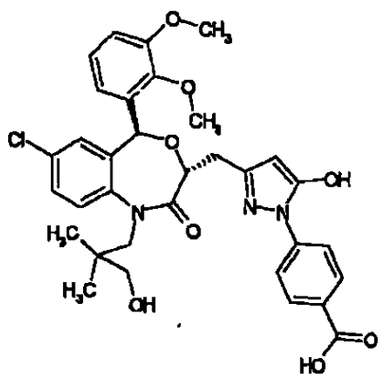
De conformidad con una manera similar a la del

ejemplo 64, se obtuvo el compuesto del título.

^{1}H-RMN (DMSO-d_6) δ: 0.92 (3H, s), 0.93 (3H, s), 1.99 (3H, s), 2.80-3.05 (2H, m), 3.52 (3H, s), 3.61-3.81 (3H, m), 3.85 (3H, s), 4.17 (1H, t, J = 6.4 Hz), 4.36 (1H, d, J = 14.1Hz), 5.43 (1H, s), 6.13 (1H, s), 7.10-7.23 (3H, m), 7.54 (1H, dd, J = 2.2, 8.6 Hz), 7.75 (d, J = 8.8 Hz), 7.84 (2H, d, J = 8.8Hz), 7.99 (d, J = 8.6 Hz), 8.32 (1H, s).

EJEMPLO 67

Acido 4-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-5-hidroxi-1H-pirazol-1-il)benzoico



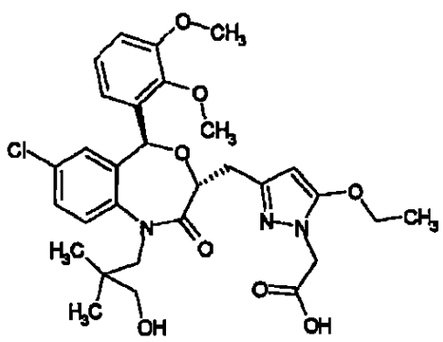
De conformidad con una manera similar a la del ejemplo 65, se obtuvo el compuesto del título.

^{1}H-RMN (DMSO-d_6) δ: 0.78 (3H, s), 0.87 (3H, s), 2.80- 3.25 (4H, m), 3.53 (3H, s), 3.69 (1H, d, J = 14.1 Hz), 3.85 (3H, s), 4.16 (1H, t, J = 6.5 Hz), 4.32 (1H, d, J = 14.1

Hz), 4.56 (1H, t, J = 4.8 Hz), 5.43 (1H, s), 6.12 (1H, s),6.39 (1H, d, J = 2.4 Hz), 7.09-7.24 (3H, m) 7.53 (1H, dd, J = 2.4, 8.6 Hz), 7.72 (1H, d, J = 8.8 HZ), 7.85 (2H, d, J = 8.8 Hz), 7.94-8.04 (2H, m).

EJEMPLO 68

Acido (3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-5-etoxi-1H-pirazol-1-il)acético



(1) Se añadió piridina (0.3 ml) a una solución de 4-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-3-oxobutanoato de etilo (2 g) obtenido en el ejemplo 26-(1) y clorhidrato de hidrazinoacetato de etilo (0.577 g) en etanol (20 ml) y la mezcla se puso a reflujo durante 3 horas. Después de concentrarse bajo presión reducida, el residuo se purificó por cromatografía en columna sobre gel de sílice para obtener (3-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-

benzoxazepin-3-il]metil}-5-etoxi-1H-pirazol-1-il)acetato de etilo (0.62 g) de una primera fracción diluida y [3-({(3R,5S)-1-[3-(acetoxi)-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il}metil)-5-hidroxi-1H-pirazol-1-il]acetato de etilo (1.2 g) de una segunda fracción diluida.

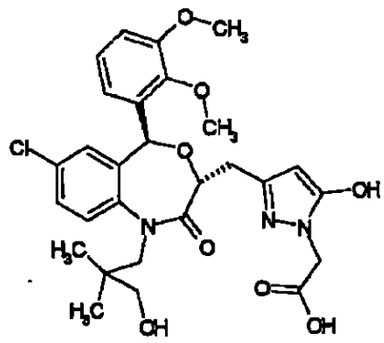
(2) Una solución acuosa 1 N de hidróxido de sodio (3.3 ml) se añadió a una solución de (3-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-5-etoxi-1H-pirazol-1-il)acetato de etilo (0.45 g) obtenido en el ejemplo 68-(1) en etanol (4.5 ml) y la mezcla se agitó durante la noche. La solución de reacción se neutralizó con ácido clorhídrico 1 N y se extrajo con cloroformo. Este extracto se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener el compuesto del título (0.38 g).

^{1}H-RMN ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 1.40 (3H, t, J = 7.0 Hz), 3.02 (1H, dd, J = 6.3, 14.8 Hz), 3.11-3.26 (2H, m), 3.37 (1H, d, J = 14.3 Hz), 3.57-3.70 (4H, m), 3.89 (3H, s), 4.05-4.23 (3H, m), 4.45 (1H, d, J = 14.3 Hz), 4.63 (2H, s), 5.49 (1H, s), 6.17 (1H, s), 6.58 (1H, d, J =

1.8 Hz), 6.98 (1H, dd, J = 2.4, 7.1 Hz), 7.11-7.23 (2H, m), 7.25-7.39 (3H, m).

EJEMPLO 69

Acido (3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-5-hidroxi-1H-pirazol-1-il)acético



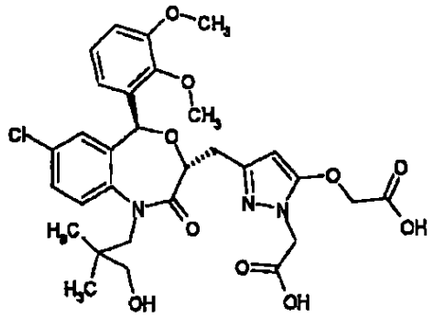
Una solución acuosa 1 N de hidróxido de sodio (0.5 ml) se añadió a una solución de [3-({(3R,5S)-1-[3-(acetiloxi)-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il}metil)-5-hidroxi-1H-pirazol-1-il]acetato de etilo (0.1 g) obtenido en el ejemplo 68-(1) en etanol (1 ml) y la mezcla se agitó durante la noche. La solución de reacción se neutralizó con ácido clorhídrico 1 N y se extrajo con cloroformo-metanol. Este extracto se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice

para obtener el compuesto del título (0.042 g).

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.03 (3H, s), 2.84-3.05 (2H, m), 3.11-3.23 (2H, m), 3.32-3.44 (2H, m), 3.62 (3H, s), 3.89 (3H, s), 4.26 (1H, t, J = 6.5 Hz), 4.34-4.49 (2H, m), 4.53-4.63 (1H, m), 6.16 (1H, s), 6.62 (1H, d, J = 2.0 Hz), 6.96-7.04 (1H, m), 7.08-7.25 (3H, m), 7.30-7.43 (3H, m).

EJEMPLO 70

Acido [5-(carboximetoxi)-3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1H-pirazol-1-il]acético



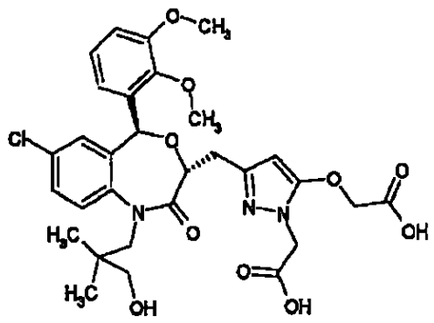
Bromoacetato de metilo (0.459 g) y carbonato de potasio (0.441 g) se añadieron a una solución de [3-({(3R,5S)-1-[3-(acetoxi)-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il}metil)-5-hidroxi-1H-pirazol-1-il]acetato de etilo (0.5 g) obtenido en el ejemplo 68-(1) en acetonitrilo (5 ml) y la

para obtener el compuesto del título (0.042 g).

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.03 (3H, s), 2.84-3.05 (2H, m), 3.11-3.23 (2H, m), 3.32-3.44 (2H, m), 3.62 (3H, s), 3.89 (3H, s), 4.26 (1H, t, J = 6.5 Hz), 4.34-4.49 (2H, m), 4.53-4.63 (1H, m), 6.16 (1H, s), 6.62 (1H, d, J = 2.0 Hz), 6.96-7.04 (1H, m), 7.08-7.25 (3H, m), 7.30-7.43 (3H, m).

EJEMPLO 70

Acido [5-(carboximetoxi)-3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1H-pirazol-1-il]acético



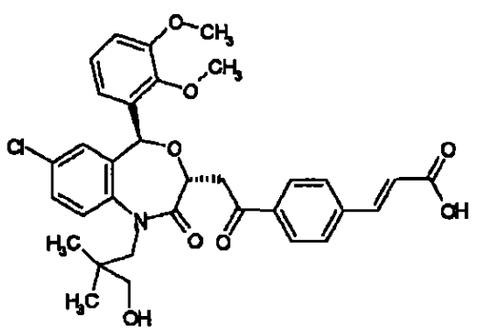
Bromoacetato de metilo (0.459 g) y carbonato de potasio (0.441 g) se añadieron a una solución de [3-({(3R,5S)-1-[3-(acetoxi)-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il}metil)-5-hidroxi-1H-pirazol-1-il]acetato de etilo (0.5 g) obtenido en el ejemplo 68-(1) en acetonitrilo (5 ml) y la

mezcla se agitó durante la noche. La solución de reacción se diluyó con acetato de etilo, se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. A este residuo se añadieron etanol (5 ml) y una solución acuosa 1 N de hidróxido de sodio (2.78 ml) y la mezcla se agitó durante la noche. La solución de reacción se neutralizó con ácido clorhídrico 1 N y se extrajo con cloroformo. Este extracto se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener el compuesto del título (0.116 g).

^{1}H-RMN (DMSO-d_6) δ: 0.76 (3H, s), 0.85 (3H, s), 2.83 (2H, m), 3.12 (2H, m), 3.51 (3H, s), 3.65 (1H, m), 3.84 (3H, s), 4.01 (1H, m), 4.32 (1H, d, J = 14.1 Hz), 4.58 (2H, s), 4.66 (2H, s), 5.47 (1H, s), 6.09 (1H, s), 6.35 (1H, d, J = 2.4 Hz), 7.12 (3H, m), 7.51 (1H, dd, J = 2.5,8.8 Hz), 7.67 (1H, d, J = 8.8 Hz).

EJEMPLO 71

Acido (2E)-3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)acrílico



(1) Se añadió cloruro de oxalilo (10 ml) a una solución de ácido (2E)-4-(bromofenil)-4-oxo-2-butenoico(24.5 g) en una mezcla de THF (200 ml) y DMF (3 gotas) y la mezcla se agitó a temperatura ambiente durante 1 hora. La solución de reacción se concentró bajo presión reducida y el residuo se disolvió en acetato de etilo (120 ml). La solución resultante se añadió gota a gota a un solvente mixto de una solución de 3-({4-cloro-2-[(S)-(2,3-dimetoxifenil)(hidroxil)-metil]fenil}amino)-2,2-dimetil-1-propanol (24.5 g) en acetato de etilo (300 ml) y una solución acuosa 1 N de hidróxido de sodio (130 ml) bajo enfriamiento con hielo, y la mezcla se agitó a 0°C durante 1 hora. La capa orgánica se lavó sucesivamente con una solución acuosa de bicarbonato de sodio y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de sodio, y después se concentró bajo presión

reducida. El residuo resultante se disolvió en etanol (240 ml), se añadió DBU (11 ml), y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua (60 ml) a la solución de reacción gradualmente y la mezcla se agitó durante 1 hora. Los cristales precipitados se filtraron y se lavaron con una solución mixta de etanol/agua = 2/1 para obtener (3R,5S)-3-[2-(4-bromofenil)-2-oxoetil]-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-1,5-dihidro-4,1-benzoxazepin-2(3H)-ona (24.5 g).

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 3.14 (1H, d, J = 12.0 Hz), 3.32 (1H, dd, J = 4.5 Hz, 17.4 Hz), 3.42 (1H, d, J= 14.4 Hz), 3.62 (3H, s), 3.64 (1H, m), 3.81(1H, m), 3.90 (3H, s), 4.48 (1H, d, J = 12.0 Hz), 4.61 (1H, q, J = 4.2 Hz), 6.19 (1H, s), 6.63 (1H, s), 6.99 (1H, dd, J = 2.4 Hz, 7.5 Hz), 7.15 (2H, m), 7.41 (2H, m), 7.61 (2H, d, J = 8.4 Hz), 7.84 (2H, d, J = 8.4 Hz).

(2) Acetato de paladio (338 mg), trifenilfosfina (788 mg), acrilato de etilo (2.2 ml) y trietilamina (3.3 ml) se añadieron a una solución de (3R,5S)-3-[2-(4-bromofenil)-2-oxoetil]-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-1,5-dihidro-4,1-benzoxazepin-2(3H)-ona (6.0 g) obtenido en el ejemplo 71-(1) en DMF (60 ml) y la mezcla se calentó a 100°C durante 20 horas bajo atmósfera de nitrógeno. Se añadió ácido clorhídrico 1 N a la solución de reacción,

seguido por extracción con acetato de etilo. El extracto se lavó con agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener (2E)-3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2,-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin- 3-il]acetil}fenil)acrilato de etilo (3.1 g).

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 1.35 (3H, t, J = 7.2 Hz), 3.14 (1H, m), 3.36 (1H, m), 3.43 (1H, m), 3.63 (3H, s), 3.64 (1H, m), 3.81 (1H, m), 3.90 (3H, s), 4.48 (1H, d, J = 13.2 Hz), 4.61 (1H, q, J = 3.6 Hz), 6.20 (1H, s), 6.53 (1H, d, J = 16.5 Hz), 6.64 (1H, m), 6.99 (1H, m), 7.16 (2H, m), 7.41 (2H, m), 7.60 (2H, d, J= 8.4 Hz), 7.68 (1H, d, J = 16.5 Hz), 7.98 (2H, d, J = 8.4 Hz).

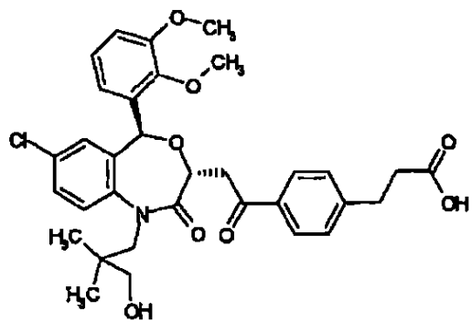
(3) Una solución acuosa 2 N de hidróxido de sodio (25 ml) se añadió a una solución de (2E)-3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2,-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)-acrilato de etilo (3.1 g) obtenido en el ejemplo 71-(2) en una mezcla de THF (100 ml) y etanol (100 ml), y la mezcla se agitó a temperatura ambiente durante 10 horas. Después de que la solución de reacción se concentró bajo presión reducida, el residuo se disolvió en agua y se lavó con éter. La capa acuosa se acidificó con ácido clorhídrico 1 N y después se

extrajo con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener ácido (2E)-3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)-acrílico (1.1 g).

^{1}H-RMN ($CDCl_3$) δ: 0.66 (3H, s), 1.05 (3H, s), 3.15 (1H, d, J = 12.0 Hz), 3.36 (1H, dd, J = 3.9 Hz, 17.1 Hz), 3.43 (1H, d, J = 15.0 Hz), 3.62 (3H, s), 3.66 (1H, m), 3.82(1H, t, J = 9.3 Hz), 3.89 (3H, s), 4.48 (1H, d, J = 14.4 Hz), 4.62 (1H, q, J= 3.9 Hz), 6.19 (1H, s), 6.52 (1H, d, J= 15.9 Hz), 6.63 (1H, s), 6.98 (1H,m), 7.15 (2H, m), 7.40 (2H, m), 7.62 (2H, d, J = 8.4 Hz), 7.77 (1H, d, J = 15.9 Hz), 7.99 (2H, d, J = 8.4 Hz).

EJEMPLO 72

Acido 3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)propiónico



(1) Se añadió níquel de Raney a una solución de (2E)-3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)acrilato de etilo (6.2 g) obtenido en el ejemplo 71-(2) en una mezcla de THF (100 ml) y etanol (50 ml), y la mezcla se agitó a temperatura ambiente durante la noche bajo atmósfera de hidrógeno. El catalizador se filtró con Celite y el filtrado se concentró bajo presión reducida para obtener 3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)propionato de etilo (6.6 g) como un cristal crudo, que se usó en el siguiente paso sin purificación.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 1.24

(3H, t, J = 7.4 Hz), 2.63 (2H, t, J = 8.4 Hz), 3.00 (2H, t, J = 8.4 Hz), 3.13 (1H, m), 3.33 (1H, m), 3.42 (1H, d, J = 14.6 Hz), 3.62 (3H, s), 3.75 (2H, m), 3.89 (3H, s), 4.21 (1H, m), 4.48 (1H, d, J = 14.6 Hz), 4.62 (1H, q, J = 4.2 Hz), 6.19 (1H, s), 6.63 (1H, m), 6.98 (1H, t, J = 5.0 Hz), 7.18 (2H, m), 7.29 (2H, d, J= 8.0 Hz), 7.40 (2H, m), 7.90 (2H, d, J = 8.0 Hz).

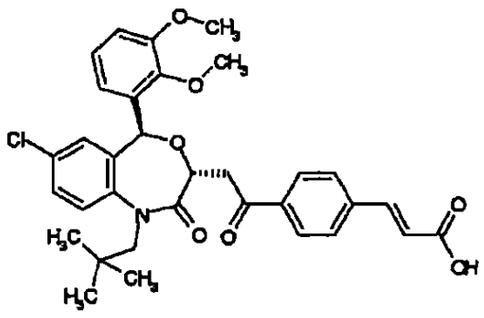
(2) Una solución acuosa 2 N de hidróxido de sodio (15 ml) se añadió a una solución de 3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)-propionato de etilo (3.5 g) obtenido en el ejemplo 72-(1) en una mezcla de THF (50 ml) y etanol (50 ml), y la mezcla se agitó a temperatura ambiente durante 2 horas. La solución de reacción se concentró bajo presión reducida y el residuo se disolvió en agua y después se lavó con éter. La capa acuosa se acidificó con ácido clorhídrico 1 N y después se extrajo con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener ácido 3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)-propiónico (2.2 g).

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 2.70

(2H, t, J = 7.8 Hz), 3.01 (2H, t, J = 7.8 Hz), 3.15 (1H, d, J = 12.0 Hz), 3.33 (1H, dd, J = 4.5 Hz, 17.4 Hz), 3.42 (1H, d, J = 17.4 Hz), 3.62 (3H, s), 3.66 (1H, m), 3.82 (1H, t, J = 8.7 Hz), 3.89 (3H, s), 4.48 (1H, d, J = 14.4 Hz), 4.62 (1H, q, J= 4.2 Hz), 6.19 (1H, s), 6.63 (1H, m), 6.99 (1H, t, J = 5.1 Hz), 7.18 (2H, d, J = 5.1 Hz), 7.30 (2H, d, J = 8.1 Hz), 7.40 (2H, m), 7.91 (2H, d, J = 8.1 Hz).

EJEMPLO 73

Acido (2E)-3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-neopentil-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)acrílico



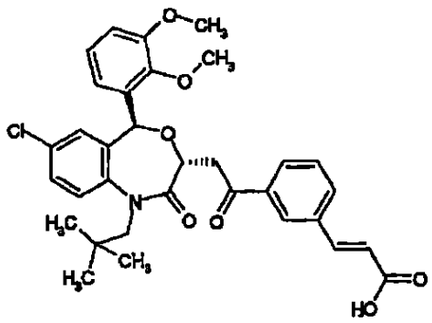
De conformidad con una manera similar a la del ejemplo 71, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 3.31 (1H, dd, J = 17.1, 4.8 Hz), 3.41 (1H, d, J = 14.1 Hz), 3.63 (3H, s), 3.80 (1H, t, J = 9.0 Hz), 3.90 (3H, s), 4.51 (1H, d, J = 14.1 Hz), 4.67 (1H, dd, J = 8.4, 4.8 Hz), 6.31 (1H, s), 6.52 (1H, d, J

= 16.2 Hz), 6.63 (1H, m), 6.98 (1H, t, J = 4.8 Hz), 7.16 (2H, d, J=4.5Hz), 7.37 (2H, m), 7.61 (2H, d, J=8.1Hz), 7.76 (1H, d, J=16.2Hz), 8.01 (2H, d, J=8.1Hz).

EJEMPLO 74

Acido (2E)-3-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-neopentil-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)acrílico

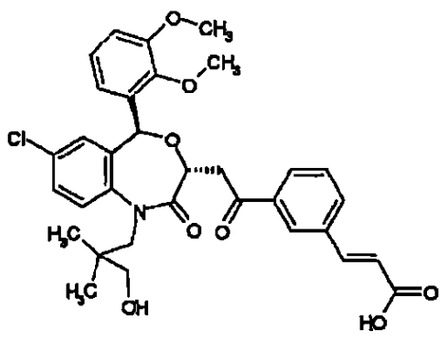


De conformidad con una manera similar a la del ejemplo 71, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.96 (9H, s), 3.37 (1H, m), 3.42 (1H, 5 d, J = 14.1 Hz), 3.64 (3H, s), 3.82 (1H, t, J = 8.1 Hz), 3.89 (3H, s), 4.52 (1H, d, J = 14.1 Hz), 4.67 (1H, dd, J = 7.8, 4.5 Hz), 6.32 (1H, s), 6.50 (1H, d, J = 16.2 Hz), 6.64 (1H, m), 6.98 (1H, m), 7.13 (2H, m), 7.36 (2H, m), 7.49 (1H, t, J = 7.5 Hz), 7.72 (1H, d, J = 7.8 Hz), 7.79 (1H, d, J = 10 16.2 Hz), 8.01 (1H, d, J = 7.5 Hz), 8.17 (1H, s).

EJEMPLO 75

Acido (2E)-3-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)acrílico

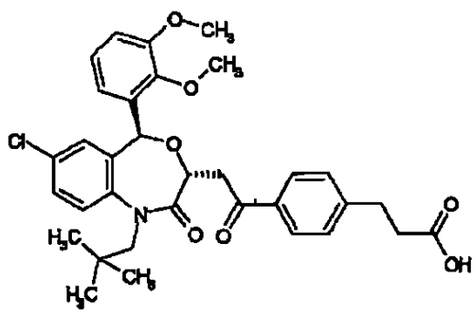


De conformidad con una manera similar a la del ejemplo 71, , se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.66 (3H, s), 1.05 (3H, s), 3.16 (1H, d, J= 12.0 Hz), 3.39 (1H, m), 3.44 (1H, d, J= 14.4 Hz), 3.63 (3H, s), 3.66 (1H, m), 3.82 (1H, m), 3.90 (3H, s), 4.49 (1H, d, J = 14.4 Hz), 4.64 (1H, q, J = 4.5 Hz), 6.20 (1H, s), 6.52 (1H, d, J = 15.9 Hz), 6.65 (1H, s), 7.00 (1H,m), 7.19 (2H, m), 7.42 (2H, m), 7.51 (1H, t, J = 7.5 Hz), 7.76 (1H, m), 7.79 (1H, d, J = 15.9 Hz), 8.01 (1H, d, J = 7.5 Hz), 8.14 (1H, s).

EJEMPLO 76

Acido 3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-neopentil-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)propiónico

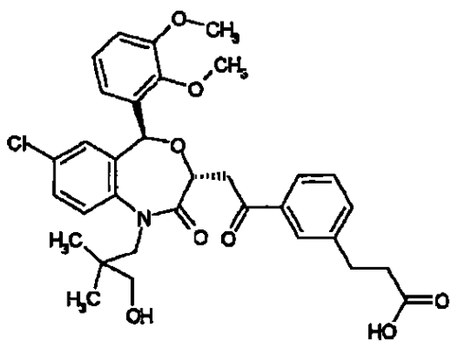


De conformidad con una manera similar a la del ejemplo 72, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (9H, s), 2.67 (2H, t, J = 7.5 Hz), 2.99 (2H, t, J = 7.5 Hz), 3.31 (1H, dd, J = 17.4 Hz, 4.5 Hz), 3.40 (1H, d, J = 13.8 Hz), 3.81 (1H, m), 3.89 (3H, s), 4.50 (1H, d, J = 13.8 Hz), 4.65 (1H, q, J = 4.8 Hz), 6.31 (1H, s), 6.63 (1H, m), 6.97 (1H, m), 7.15 (2H, m), 7.28 (2H, d, J = 8.1 Hz), 7.37 (2H, m), 7.92 (2H, d, J = 8.1 Hz).

EJEMPLO 77

Acido 3-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)propiónico

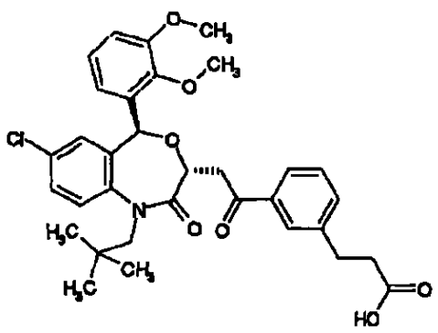


De conformidad con una manera similar a la del ejemplo 72, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.66 (3H, s), 1.03 (3H, s), 2.65 (2H, t, J = 7.5 Hz), 2.98 (2H, t, J = 7.5 Hz), 3.19 (1H, d, J = 12.0 Hz), 3.37 (1H, dd, J = 4.2 Hz, 16.8 Hz), 3.44 (1H, d, J = 17.4 Hz), 3.62 (3H, s), 3.66 (1H, m), 3.86 (1H, t, J = 9.6 Hz), 3.88 (3H, s), 4.47 (1H, d, J = 12.0 Hz), 4.63 (1H, q, J = 4.5 Hz), 6.19 (1H, s), 6.64 (1H, m), 6.98 (1H, m), 7.18 (2H, m), 7.41 (4H, m), 7.78 (2H, m).

EJEMPLO 78

Acido 3-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-neopentil-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)propiónico

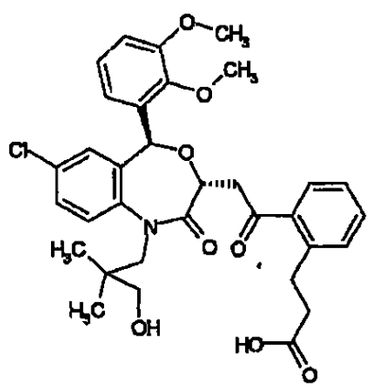


De conformidad con una manera similar a la del ejemplo 72, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 2.66 (2H, t, J = 7.5 Hz), 2.98 (2H, t, J = 7.5 Hz), 3.34 (1H, dd, J = 17.1 Hz, 4.8 Hz), 3.40 (1H, d, J = 14.1 Hz), 3.63 (3H, s), 3.65 (1H, m), 3.78 (1H, t, J = 7.8 Hz), 3.88 (3H, s), 4.52 (1H, d, J = 14.1 Hz), 4.65 (1H, q, J = 3.9 Hz), 6.31 (1H, s), 6.63 (1H, m), 6.98 (1H, m), 7.17 (2H, m), 7.38 (4H, m), 7.83 (2H, m).

EJEMPLO 79

Acido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)propiónico

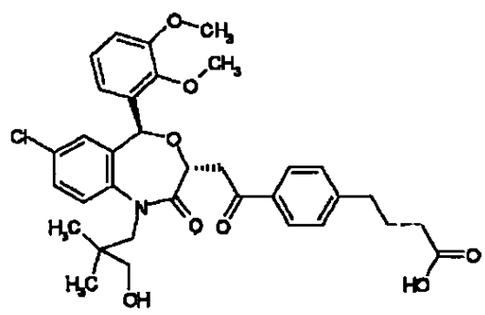


De conformidad con una manera similar a la del ejemplo 72, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.66 (3H, s), 1.04 (3H, s), 2.66 (2H, m), 3.08 (2H, m), 3.20 (1H, d, J = 12.0 Hz), 3.31 (1H, dd, J = 4.5 Hz, 17.7 Hz), 3.45 (1H, d, J = 17.4 Hz), 3.61 (3H, s), 3.63 (1H, m), 3.77 (1H, m), 3.87 (3H, s), 4.47 (1H, d, J = 12.0 Hz), 4.63 (1H, q, J = 4.2 Hz), 6.18 (1H, s), 6.65 (1H, m), 6.98 (1H, m), 7.18 (2H, m), 7.29 (2H, m), 7.38 (3H, m), 7.80 (1H, d, J = 8.1 Hz).

EJEMPLO 80

Acido 4-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)butanoico

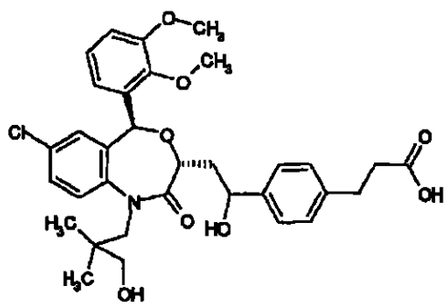


De conformidad con una manera similar a la del ejemplo 72, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 1.96 (2H, m), 2.35 (2H, t, J = 6.9 Hz), 2.71 (2H, t, J = 7.8 Hz), 3.16 (1H, d, J = 12.0 Hz), 3.34 (1H, dd, J = 4.5 Hz, 17.4 Hz), 3.42 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.63 (1H, m), 3.81 (1H, t, J = 8.7 Hz), 3.88 (3H, s), 4.48 (1H, d, J = 14.1 Hz), 4.62 (1H, q, J = 3.9 Hz), 6.18 (1H, s), 6.62 (1H, m), 6.97 (1H, m), 7.17 (2H, m), 7.29 (2H, m), 7.39 (2H, m), 7.89 (2H, d, J = 8.1 Hz) .

EJEMPLO 81

Acido 3-(4-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-1-hidroxietil}fenil)propiónico



(1) Se añadió cloruro de acetilo (0.4 ml) a una solución de 3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidr0-4,1-benzoxazepin-3-il]acetil}fenil)propionato de etilo (3.0 g) obtenido en el ejemplo 72-(1) en una mezcla de THF (50 ml) y piridina (0.8 ml), y la mezcla se agitó a temperatura ambiente durante 2 horas. Se añadió agua a la solución de reacción, seguido por extracción con acetato de etilo. La capa orgánica resultante se lavó sucesivamente con ácido clorhídrico diluido, una solución acuosa saturada de $NaHCO_3$ y agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener 3-(4-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)propionato de etilo (2.7 g) como un aceite.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.02 (3H, s), 1.26 (3H, t, J = 7.2 Hz), 2.04 (3H, s), 2.62 (2H, t, J = 7.8 Hz), 2.99 (2H, t, J = 7.8 Hz), 3.30 (1H, dd, J = 4.8, 17.4 Hz), 3.60 (1H, m), 3.61 (3H, s), 3.76 (2H, m), 3.89 (3H, s), 4.11 (2H, q, J = 7.2 Hz), 4.56 (1H, d, J = 14.4 Hz), 4.62 (1H, q, J= 4.8 Hz), 6.28 (1H, s), 6.65 (1H, m), 6.97 (1H, m), 7.16 (2H, m), 7.26 (2H, m), 7.36 (2H, m), 7.89 (2H, d, J = 8.4 Hz).

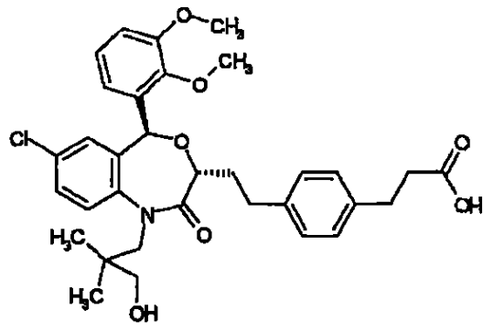
(2) Borhidriro de sodio (40 mg) y metanol (2 ml) se añadieron sucesivamente a una solución de 3-(4-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-0XO-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenıl)-propionato de etilo (0.2 g) obtenido en el ejemplo 81-(1) en THF (5 ml) y la mezcla se agitó a temperatura ambiente durante 30 minutos. Después de que se añadió ácido clorhídrico 1 N, la solución de reacción se extrajo con acetato de etilo. La capa orgánica resultante se lavó sucesivamente con ácido clorhídrico diluido y agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. Después de que el residuo resultante se disolvió en THF (5 ml) y etanol (5 ml}, una solución acuosa 2 N de hidróxido de sodio (2.5 ml) se añadió a la misma y la mezcla se agitó a temperatura ambiente durante 2 horas. La solución de reacción se acidificó con ácido clorhídrico

diluido y después se extrajo con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener ácido 3-(4-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-1-hidroxietil}fenil)propiónico (83 mg) como polvo.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.27 (2H, m), 2.64 (2H, m), 2.93 (2H, m), 3.16 (1H, d, J = 12.0 Hz), 3.37 (1H, d, J = 14.1 Hz), 3.61 (2H, m), 3.63 (3H, s), 3.90 (3H, s), 4.14 (1H, m), 4.47 (1H, d, J = 14.1 Hz), 4.83 (1H, m), 6.18 (1H, s), 6.64 (1H, m), 7.00 (1H, m), 7.1-7.4 (8H, m).

EJEMPLO 82

Acido 3-(4-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}fenil)propiónico



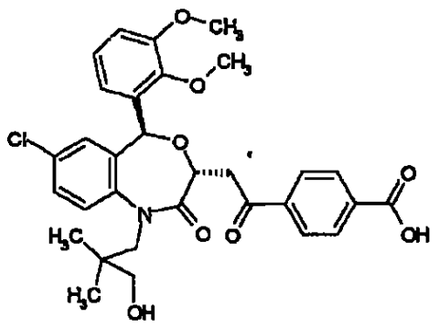
Se añadió cloruro de tionilo (0.2 ml) a una solución de 3-(4-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)propionato de etilo (1.2 g) obtenido en el ejemplo 81-(1) en una mezcla de diclorometano (30 ml) y piridina (0.5 ml), y la mezcla se agitó a temperatura ambiente durante 1 hora. Después de que se añadió ácido clorhídrico diluido, la solución de reacción se extrajo con diclorometano. La capa orgánica se lavó sucesivamente con ácido clorhídrico diluido, una solución acuosa saturada de $NaHCO_3$ y agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se disolvió en ácido acético (10 ml), se añadió un polvo de zinc (2.5 g) se añadió al mismo, y la mezcla se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se filtró con Celite y el filtrado se concentró bajo presión reducida. Una solución acuosa saturada de $NaHCO_3$ se añadió al residuo resultante y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice. El aceite resultante se disolvió en THF (10 ml) y etanol (10 ml), una solución acuosa 2N de NaOH (5.0 ml) se añadió al mismo, y la mezcla se agitó a temperatura ambiente durante 2 horas. La solución de

reacción se acidificó con ácido clorhídrico diluido y después se extrajo con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener ácido 3-(4-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}fenil)propiónico (115 mg) como polvo.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.19 (2H, m), 2.63 (2H, m), 2.90 (2H, m), 3.15 (1H, d, J = 11.7 Hz), 3.37 (1H, d, J = 14.1 Hz), 3.62 (4H, m), 3.63 (3H, s), 3.81 (2H, m), 3.90 (3H, s), 4.45 (1H, d, J = 14.1 Hz), 6.18 (1H, s), 6.64 (1H, m), 7.00 (1H, m), 7.1-7.4 (8H, m).

EJEMPLO 83

Acido 4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}benzoico



Acetato de paladio (655 mg), 1,1'-

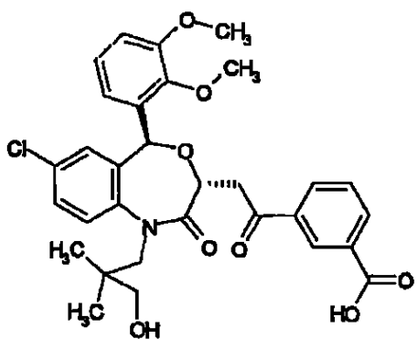
bis(difenilfosfino)ferroceno (1.6 g) y trietilamina (4.0 ml) se añadieron a una solución de (3R,5S)-3-[2-(4-bromofenil)-2-oxoetil]-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-1,5-dihidro-4,1-benzoxazepin-2-(3H)-ona (6.0 g) obtenido en el ejemplo 71-(1) en una mezcla de DMF (60 ml) y metanol (30 ml), y la mezcla se calentó a 60°C durante 20 horas bajo atmósfera de monóxido de carbono. Después de que se añadió ácido clorhídrico 1 N, la solución de reacción se extrajo con acetato de etilo. El extracto se lavó con agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice y el aceite resultante se disolvió en una mezcla de THF (100 ml) y etanol (100 ml). A la misma se añadió una solución acuosa 2N de NaOH (25 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. La solución de reacción se acidificó con ácido clorhídrico diluido y después se extrajo con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener ácido 4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}benzoico(1.7 g).

^{1}H-RMN ($CDCl_3$) δ: 0.66 (3H, s), 1.05 (3H, s), 3.16 (1H, d, J = 11.7 Hz), 3.39 (1H, dd, J = 3.9 Hz, 17.7 Hz),

3.43 (1H, d, J= 13.8 Hz), 3.62 (3H, s), 3.65 (1H, m), 3.85 (1H, t, J=7.8Hz), 3.89 (3H, s), 4.49 (1H, d, J=14.4Hz), 4.63 (1H, q, J = 4.5 Hz), 6.19 (1.H, s), 6.63 (1H, m), 6.98 (1H, m), 7.16 (2H, m), 7.41 (2H, m), 7.04 (2H, d, J = 8.4 Hz), 8.17 (2H, d, J= 8.4 Hz).

EJEMPLO 84

Acido 3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)acetil}benzoico

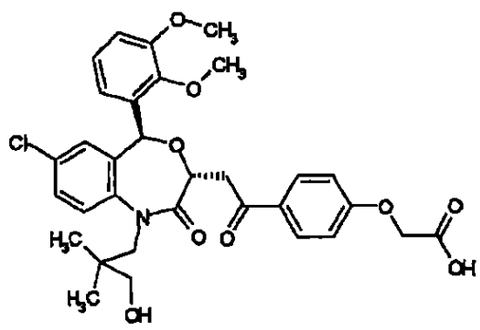


De conformidad con una manera similar a la del ejemplo 83, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.66 (3H, s), 1.06 (3H, s), 3.17 (1H, d, J = 11.7 Hz), 3.42 (1H, m), 3.63 (3H, s), 3.67 (1H, m), 3.90 (3H, s), 3.93 (1H, m), 4.50 (1H, d, J = 14.7 Hz), 4.66 (1H, q, J=4.5Hz), 6.21 (1H, s), 6.65 (1H, m), 7.00 (1H, m), 7.19 (2H, m), 7.42 (2H, m), 7.59 (1H, t, J = 7.8 Hz), 8.20 (1H, m), 8.30 (1H, m), 8.71 (1H, m).

EJEMPLO 85

Acido (4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenoxi)acético



(1) De conformidad con una manera similar a la del ejemplo 71-(1), (3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-3-[2-(4-hidroxifenil)-2-oxoetil]-1,5-dihidro-4,1-benzoxazepin-2(3H)-ona se sintetizó con el uso de ácido (2E)-4-(acetoxifenil)-4-oxo-2-butenoico como el material de partida.

^{1}H-RMN ($CDCl_3$) δ: 0.66 (3H, s), 1.05 (3H, s), 3.17 (1H, m), 3.28 (1H, dd, J = 4.5 Hz, 16.8 Hz), 3.43 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.65 (1H, m), 3.79 (1H, m), 3.89 (3H, s), 4.47 (1H, d, J = 14.1 Hz), 4.62 (1H, m), 6.18 (1H, s), 6.62 (1H, m), 6.84 (2H, d, J= 8.7 Hz), 6.97 (1H, t, J = 4.5 Hz), 7.17 (2H, m), 7.39 (2H, m), 7.87 (2H, d, J= 8.7 Hz).

(2) K_2CO_3 (0.5 g) y bromoacetato de etilo (0.22 ml) se añadieron a una solución de (3R,5S)-7-cloro-5-(2,3-

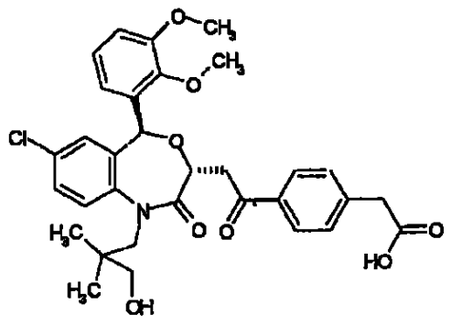
dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-3-[2-(4-hidroxifenil)-2-oxoetil]-1,5-dihidro-4,1-benzoxazepin-2(3H)-ona (1.0 g) obtenido en el ejemplo 85-(1) en DMF (20 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. Después de que se añadió ácido clorhídrico 1 N, la solución de reacción se extrajo con acetato de etilo. El extracto se lavó con agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. Después de que el residuo resultante se disolvió en una mezcla de THF (10 ml) y etanol (10 ml), una solución acuosa 2N de NaOH (5 ml) se añadió a la misma y la mezcla se agitó a temperatura ambiente durante 2 horas. La solución de reacción se acidificó con ácido clorhídrico diluido y después se extrajo con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener ácido (4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenoxi)acético (0.82 g) como polvo.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 3.20 (1H, d, J = 12.0 Hz), 3.31 (1H, dd, J = 3.9 Hz, 17.1 Hz), 3.42 (1H, d, J= 15.0 Hz), 3.62 (3H, s), 3.66 (1H, m), 3.81 (1H, m), 3.90 (3H, s), 4.46 (1H, d, J = 14.7 Hz), 4.61 (1H, m), 4.71 (2H, s), 6.17 (1H, s), 6.63 (1H, m), 6.94 (2H, d, J

= 9.0 Hz), 7.00 (1H, m), 7.17 (2H, m), 7.40 (2H, m), 7.95 (2H, d, J = 9.0 Hz).

EJEMPLO 86

Acido (4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)acetil}fenil)acético



(1) De conformidad con una manera similar a la del ejemplo 71-(1), (4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)acetato de etilo se sintetizó con el uso de ácido (2E)-4-[4-(2-etoxi-2-oxoetil)fenil]-4-oxo-2-butenoico como el material de partida.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 1.25 (3H, t, J= 7.2 Hz), 3.14 (1H, m), 3.35 (1H, m), 3.43 (1H, d, J = 15.3 Hz), 3.65 (3H, s), 3.65 (3H, m), 3.81 (1H, m), 3.90 (3H, s), 4.15 (2H, q, J = 7.2 Hz), 4.49 (1H, d, J = 15.3 Hz), 4.63 (1H, m), 6.20 (1H, s), 6.64 (1H, m), 6.99 {1H, m), 7.18

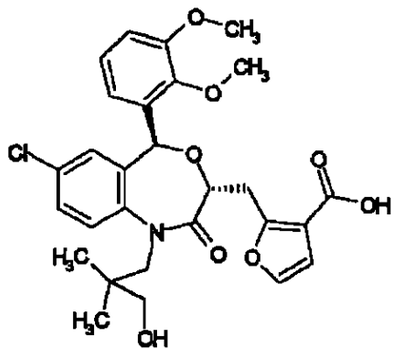
(2H, m), 7.40 (4H, m), 7.90 (2H, m).

(2) Una solución acuosa 2N de NaOH (30 ml) se añadió a una solución de (4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)acetato de etilo (7.1 g) obtenido en el ejemplo 86-(1) en una mezcla de THF (50 ml) y etanol (100 ml), y la mezcla se agitó a temperatura ambiente durante 2 horas. La solución de reacción se acidificó con ácido clorhídrico diluido y después se extrajo con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener ácido (4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)acético (4.8 g).

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 3.16 (1H, d, J = 11.7 Hz), 3.34 (1H, dd, J = 4.2 Hz, 17.4 Hz), 3.42 (1H, d, J = 14.1 Hz), 3.62 (3H, s), 3.65 (1H, m), 3.69 (2H, s), 3.81 (1H, m), 3.89 (3H, s), 4.47 (1H, d, J = 14.1 Hz), 4.62 (1H, m), 6.18 (1H, s), 6.64 (1H, m), 6.99 (1H, m), 7.17 (2H, m), 7.45 (4H, m), 7.89 (2H, m) .

EJEMPLO 87

Acido 2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-3-furancarboxílico



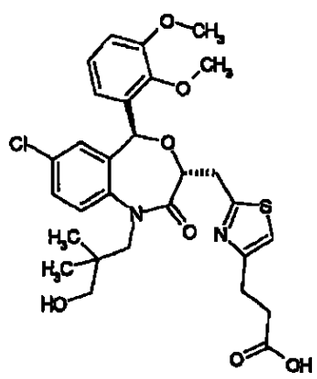
4-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-3-oxobutanoato de etilo (1.2. g) se disolvió en tolueno (5 ml), y DBU (0.3 ml) se añadió después al mismo. Después de que se añadió una solución acuosa al 40% de cloroacetoaldehído (0.4 ml) bajo enfriamiento con hielo, la mezcla se agitó a temperatura ambiente durante 1 hora. Después de añadir agua, la solución de reacción se extrajo con tolueno. La capa orgánica resultante se concentró bajo presión reducida. El residuo resultante se disolvió en tolueno (20 ml), se añadió una cantidad catalítica de ácido p-toluensulfónico, y la mezcla se calentó a 100°C durante 2 horas. La solución de reacción se concentró y después se purificó por columna sobre gel de sílice. El residuo

resultante se disolvió en una mezcla de THF (5 ml) y metanol (20 ml), se añadió una solución acuosa 2N de NaOH (5 ml), y la mezcla se agitó a temperatura ambiente durante la noche. La solución de reacción se acidificó con ácido clorhídrico diluido y después se extrajo con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener ácido 2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-3-furancarboxílico(26 mg).

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H,s), 1.06 (3H,s), 3.16 (1H, d, J= 11.7 Hz), 3.40 (1H, d, J = 14.7 Hz), 3.57 (3H,m), 3.60 (3H,s), 3.87 (3H,s), 4.29 (1H, m), 4.50 (1H,d,J= 14.7 Hz), 6.17 (1H, s), 6.53(1H, s), 6.70 (1H, m), 6.99 (1H, d, J = 8.4 Hz), 6.95 (1H, d, J = 9.3 Hz), 7.12 (1H, t, J = 8.1 Hz), 7.31 (3H,m).

EJEMPLO 88

Acido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dirnetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-4-il)propiónico



(1) Se añadió 10% de Pd sobre carbón (47 mg) a una solución de (2E)-3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetil-propil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)metil}-1,3-tiazol-4-il)acrilato de etilo (0.47 g, 0.72 mmoles) obtenido como en el ejemplo 19-(1) en THF (5 ml) bajo atmósfera de nitrógeno, y después se introdujo hidrógeno. La mezcla se agitó a temperatura ambiente durante 48 horas y después a 40°C durante 12 horas. El catalizador se filtró con el uso de Celite y el filtrado se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (73:27-65:35)] para obtener 3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-

tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-4-il)propionato de etilo (0.38 g, 0.58 mmoles, 81%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.03 (3H, s), 1.21 (3H, t, J = 7.2 Hz), 2.03 (3H, s), 2.67 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.45 (1H, dd, J = 7.2, 15.0 Hz), 3.54 (1H, d, J = 14.4 Hz), 3.56 (1H, dd, J = 5.7, 15.0 Hz), 3.62 (3H, s), 3.73 (1H, d, J = 11.1 Hz), 3.85 (1H, d, J = 11.1 Hz), 3.89 (3H, s), 4.11 (2H, q, J = 7.2 Hz), 4.29 (1H, dd, J = 5.7, 7.2 Hz), 4.56 (1H, d, J = 14.4 Hz), 6.31 (1H, s), 6.60 (1H, d, J = 2.4 Hz), 6.82 (1H, s), 6.98 (1H, dd, J = 2.4,7.2 Hz), 7.10-7.20 (2H, m), 7.28 (1H, d, J = 8.4 Hz), 7.33 (1H, dd, J = 2.4, 8.4 Hz).

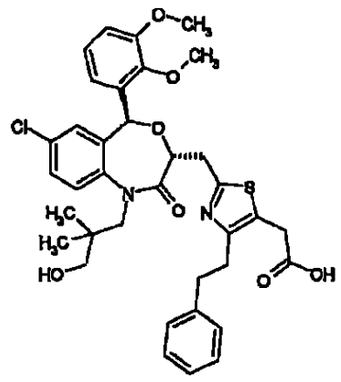
(2) Una mezcla de 3-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-4-il)propionato de etilo (0.35 g, 0.53 mmoles) obtenido en el ejemplo 88-(1), una solución acuosa 1 N de hidróxido de sodio (3.0 ml) y etanol (10 ml) se agitó a temperatura ambiente durante 2 horas. Esta mezcla se acidificó con ácido clorhídrico acuoso 1 N (3.5 ml) y acetato de etilo (80 ml) se añadió a la misma. La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para

obtener ácido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-4-il)propiónico (0.3 g, 0.51 mmoles, 96%) como polvo no cristalino incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 2.69-2.80 (2H, m), 3.02 (2H, t, J = 7.2 Hz), 3.16 (1H, d, J = 12.0 Hz), 3.41 (1H, d, J = 14.7 Hz), 3.48 (1H, dd, J = 6.6, 15.3 Hz), 3.59-3.70 (2H, m), 3.62 (3H, s), 3.90 (3H, s), 4.33 (1H, t, J = 6.6 Hz), 4.47 (1H, d, J = 14.7 Hz), 6.21 (1H, s), 6.59 (1H, d, J = 2.7 Hz), 6.89 (1H, s), 7.00 (1H, dd, J = 2.4 , 7.8 Hz), 7.10- 7.22 (2H, m), 7.38-8.01 (2H, m).

EJEMPLO 89

Acido [2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-4-(2-feniletil)-1,3-tiazol-5-il]acético

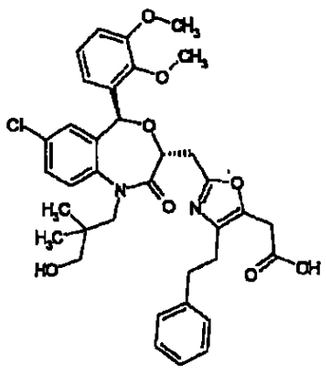


De conformidad con una manera similar a la del ejemplo 1, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.81-2.92 (4H, m), 3.17 (1H, d, J = 11.4 Hz), 3.36 (1H, d, J = 14.4 Hz), 3.40-3.70 (3H, m), 3.46 (2H, s), 3.61 (1H, d, J = 11.7 Hz), 3.87 (3H, s), 4.34 (1H, t, J = 6.9 Hz), 4.47 (1H, d, J = 14.4 Hz), 6.20 (1H, s), 6.58 (1H, d, J = 2.4 Hz), 6.90-7.06 (3H, m), 7.09-7.38 (7H, m).

EJEMPLO 90

Acido [2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-4-(2-feniletil)-1,3-oxazol-5-il]acético



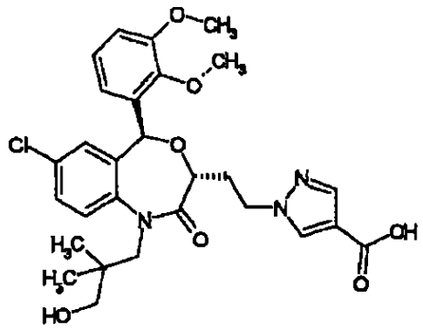
De conformidad con una manera similar a la del ejemplo 27, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.04 (3H, s), 2.68

(2H, t, J = 7.5 Hz), 2.87 (2H, t, J = 7.5 Hz), 3.16 (1H, d, J = 12.0 Hz), 3.20-3.42 (3H, m), 3.36 (2H, s), 3.61 (3H, s), 3.62 (1H, d, J = 12.0 Hz), 3.87 (3H, s), 4.40-4.51 (2H, m), 6.18 (1H, s), 6.59 (1H, d, J = 2.1 Hz), 6.95 (1H, dd, J = 1.8, 8.1 Hz), 7.02-7.29 (8H, m), 7.37 (1H, dd, J = 2.1, 8.4 Hz).

EJEMPLO 91

Acido 1-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-pirazol-4-carboxílico



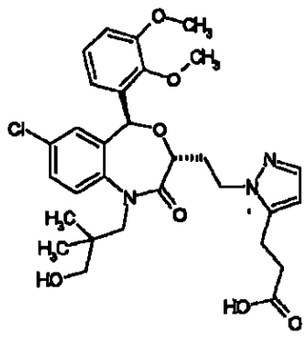
De conformidad con una manera similar a la del ejemplo 50, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.29-2.50 (2H, m), 3.15 (1H, d, J = 12.3 Hz), 3.36 (1H, d, J = 13.8Hz), 3.607 (1H, d, J = 12.3Hz), 3.61 (3H, s), 3.78 (1H, t, J = 7.5 Hz), 3.89 (3H, s), 4.25-4.43 (2H, m), 4.45 (1H, d, J = 13.8 Hz), 6.15 (1H, s), 6.61 (1H, d, J = 2.4 Hz), 7.00

(1H, dd, J = 2.4, 7.2 Hz), 7.15-7.26 (2H, m), 7.28 (1H, d, J = 8.4 Hz), 7.34 (1H, dd, J = 2.4, 8.4 Hz), 7.85 (1H, s), 7.88 (1H, s).

EJEMPLO 92

Acido 3-(1-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-pirazol-5-il)propiónico



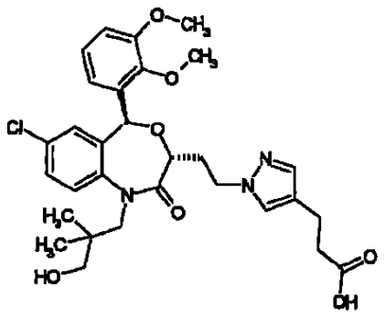
De conformidad con una manera similar a la del ejemplo 88 con el uso de ácido 1-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-pirazol-5-carboxílico obtenido en el ejemplo 50, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 2.20-2.43 (2H, m), 2.69 (2H, t, J = 8.1 Hz), 2.87-2.98 (2H, m), 3.15 (1H, d, J = 12.3 Hz), 3.35 (1H, d, J = 14.1 Hz), 3.605 (3H, s), 3.613 (1H, d, J = 12.3 Hz), 3.88 (1H, t, J = 6.3

Hz), 3.89 (3H, s), 4.20-4.30 (2H, m), 4.41 (1H, d, J = 14.1 Hz), 5.97 (1H, d, J = 1.8 Hz), 6.13 (1H, s), 6.61 (1H, d, J = 2.1 Hz), 6.99 (1H, dd, J = 2.1, 7.8 Hz), 7.17-7.40 (5H, m).

EJEMPLO 93

Acido 3-(1-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-pirazol-4-il)propiónico

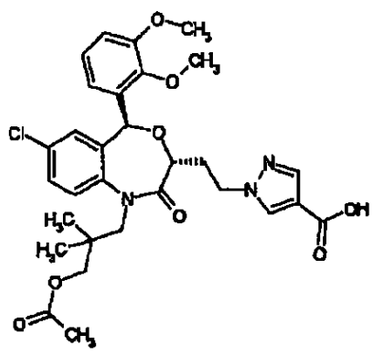


De conformidad con una manera similar a la del ejemplo 92, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 2.23-2.40 (2H, m), 2.50 (2H, t, J = 7.2 Hz), 2.71 (2H, t, J = 7.2 Hz), 3.15 (1H, d, J = 11.7 Hz), 3.35 (1H, d, J = 14.4 Hz), 3.607 (1H, d, J = 11.7 Hz), 3.61 (3H, s), 3.72 (1H, t, J = 6.6 Hz), 3.90 (3H, s), 4.18-4.37 (2H, m), 4.42 (1H, d, J = 14.4 Hz), 6.14 (1H, s), 6.61 (1H, d, J = 2.1 Hz), 6.96-7.03 (1H, m), 7.15-7.30 (5H, m), 7.35 (1H, dd, J = 2.1, 8.7 Hz).

EJEMPLO 94

Acido 1-{2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-pirazol-4-carboxílico

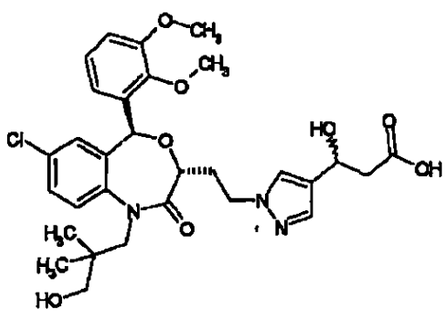


De conformidad con una manera similar a la del ejemplo 14, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 2.03 (3H, s), 2.30-2.50 (2H, m), 3.52 (1H, d, J = 14.1 Hz), 3.62 (3H, s), 3.72 (1H, d, J = 10.8 Hz), 3.77 (1H, dd, J = 5.4, 7.2 Hz), 3.86 (1H, d, J = 10.8 Hz), 3.90 (3H, s), 4.25-4.43 (2H, m), 4.56 (1H, d, J = 14.1 Hz), 6.26 (1H, s), 6.64 (1H, d, J = 2.7 Hz), 6.97-7.05 (1H, m), 7.17-7.25 (2H, m), 7.26 (1H, d, J = 9.0 Hz), 7.33 (1H, dd, J = 2.7, 9.0 Hz), 7.86 (1H, s), 7.90 (1H, s).

EJEMPLO 95

Acido 3-(1-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-pirazol-4-il)-3-hidroxipropiónico

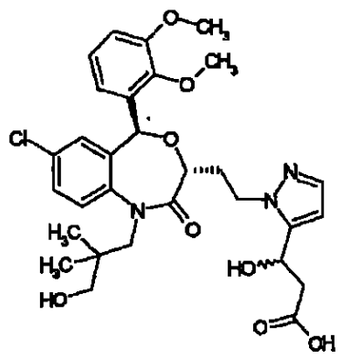


De conformidad con una manera similar a la del ejemplo 18, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 2.28-2.40 (2H, m), 2.63-2.80 (2H, m), 3.15 (1H, d, J = 12.0 Hz), 3.35 (1H, d, J = 14.1 Hz), 3.55-3.62 (1H, m), 3.61 (3H, s), 3.76-3.82 (1H, m), 3.90 (3H, s), 4.19-4.44 (3H, m), 5.00-5.09 (1H, m), 6.13 (1H, s), 6.62 (1H, d, J = 2.1 Hz), 6.98-7.02 (1H, m), 7.19-7.22 (6H, m).

EJEMPLO 96

Acido 3-(1-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-Pirazol-5-il)-3-hidroxipropiónico

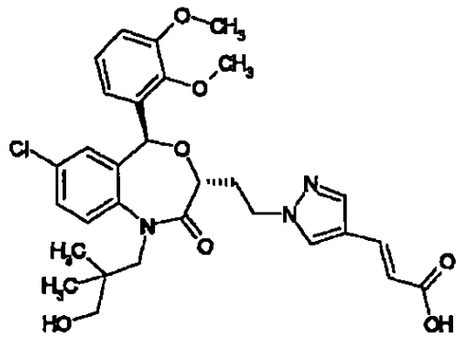


De conformidad con una manera similar a la del ejemplo 18, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.62 (3/2H, s), 0.63 (3/2H, s), 1.02 (3/2H, s), 1.03 (3/2H, s), 2.20-2.40 (1H, m), 2.21-2.43 (1H, m), 2.79-3.03 (2H, m), 3.148 (1/2H, d, J = 12.0 Hz), 3.158 (1/2H, d, J = 12.0 Hz), 3.31 (1/2H, d, J = 14.1 Hz), 3.35 (1/2H, d, J = 14.1 Hz), 3.50-3.63 (1H, m), 3.59 (3/2H, s), 3.60 (3/2H, s), 3.88 (3H, s), 3.91-4.03 (1H, m), 4.20-4.51 (3H, m), 5.18-5.28 (1H, m), 6.09 (1/2H, s), 6.11 (1/2H, s), 6.139 (1/2H, s), 6.144 (1/sH, s), 6.61 (1H, d, J = 1.8 Hz), 6.96-7.01 (1H, m), 7.15-7.40 (5H, m).

EJEMPLO 97

Acido (2E)-3-(1-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1H-pirazol-4-il)acrílico



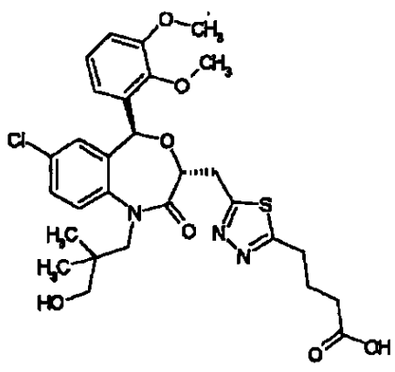
De conformidad con una manera similar a la del ejemplo 19, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.29-2.49 (2H, m), 3.15 (1H, d, J = 12.3 Hz), 3.36 (1H, d, J = 13.5 Hz), 3.61 (1H, d, J = 12.3 Hz), 3.62 (3H, s), 3.80 (1H, dd, J = 5.4,7.2 Hz), 3.90 (3H, s), 4.28-4.40 (2H, m), 4.46 (1H, d, J = 13.5 Hz), 6.09 (1H, d, J = 15.9 Hz), 6.16 (1H, s), 6.62 (1H, d, J = 2.4 Hz), 7.03 (1H, dd, J = 2.1, 7.2 Hz), 7.18-7.24 (2H, m), 7.29 (1H, d, J = 8.4 Hz), 7.36 (1H, dd, J = 2.4, 8.4 Hz), 7.55 (1H, s), 7.57 (1H, d, J = 15.9 Hz), 7.62 (1H, s).

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EJEMPLO 98

Acido 4-(5-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil-1-(3-hidroxi-2,2-dimetılpropil}-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il}-1,3,4-tiadiazol-2-il]butanoico

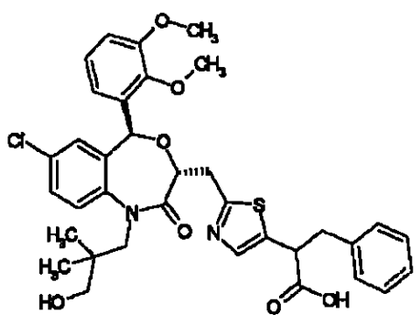


De conformidad con una manera similar a la del ejemplo 56, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 2.15 (2H, quintuplete, J = 7.2 Hz), 2.49 (2H, t, J = 7.2 Hz), 3.16 (2H, t, J = 7.2 Hz), 3.10-3.20 (1H, m), 3.38 (1H, d, J = 13.8 Hz), 3.53 (1H(dd, J = 6.6, 15.3 Hz), 3.58-3.70 (2H, m), 3.62 (3H, s), 4.39 (1H, t, J = 6.6 Hz), 4.45 (1H, d, J = 13.8 Hz), 6.20 (1H, s), 6.59 (1H, d, J= 2.1 Hz), 6.99 (1H, dd, J = 1.8, 8.1 Hz), 7.12 (1H, dd, J = 1.8, 8.2 Hz), 7.19 (1H, t, J = 8.1 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.36 (1H, dd, J = 2.1, 8.4 Hz).

EJEMPLO 99

Acido 2-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiadol-5-il)-3-fenilpropiónico



(1) Se añadió ácido sulfúrico concentrado (0.1 ml) a una solución de ácido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acético (7.5 g, 13.0 mmoles) obtenido en el ejemplo 1 en etanol (75 ml) y la mezcla se calentó a reflujo durante 24 horas con agitación. Después de reposar hasta enfriamiento a temperatura ambiente, la mezcla se concentró bajo presión reducida y acetato de etilo (400 ml) se añadió al residuo. La capa orgánica se lavó con una solución acuosa saturada de carbonato de sodio carbonate, agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio y después se concentró bajo presión reducida. El residuo resultante se disolvió en DMF (70 ml). Imidazol (1.06 g, 15.7 mmoles) y ter-butildimetilclorosilano (2.36 g, 15.7

mmoles) se añadieron al mismo y la mezcla se agitó durante 14 horas. Después de añadir agua (50 ml), la solución de reacción se extrajo con acetato de etilo (350 ml) y la capa orgánica se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (1:1)] para obtener (2-{[(3R,5S)-1-(3-{[ter-butil(dimetil)silil]oxi}-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acetato de etilo (7.97 g, 11.1 mmoles, 85%) como un polvo no cristalino amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 0.09 (3H, s), 0.11 (3H, s), 0.96 (3H, s), 0.98 (9H, s), 1.10 (3H, s), 1.39 (3H, t, J = 6.9 Hz), 3.29 (1H, d, J = 9.9 Hz), 3.34 (1H, d, J = 9.9 Hz), 3.55 (1H, dd, J = 7.2, 15.0 Hz), 3.67 (1H, dd, J = 6.0, 15.0 Hz), 3.72 (3H, s), 3.78 (1H, d, J = 13.8 Hz), 3.89 (2H, s), 3.99 (3H, s), 4.30 (2H, q, J = 6.9 Hz), 4.43 (1H, dd, J = 6.0, 7.2 Hz), 4.50 (1H, d, J = 13.8 Hz), 6.38 (1H, s), 6.65-6.68 (1H, m), 7.07 (1H, dd, J = 2.4, 6.9 Hz), 7.20-7.31 (2H, m), 7.36-7.40 (2H, m), 7.52-7.54 (1H, m).

(2) Se añadió bistrimetilsililamida de litio (0.63 ml, 0.7 mmoles) gota a gota a una solución de (2-{[(3R,5S)-1-

(3-{[ter-butil(dimetil)silil]oxi}-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acetato de etilo (0.5 g, 0.70 mmoles) obtenido en el ejemplo 99-(1) en THF (5 ml) a -78°C bajo atmósfera de nitrógeno. Después de agitarse a la misma temperatura durante 1 hora, se añadió bromuro de bencilo (0.08 ml, 0.7 mmoles) gota a gota a la misma y la mezcla se agitó a -50°C durante 5 horas. Después de que se añadió una solución acuosa saturada de cloruro de amonio (3 ml), la mezcla se extrajo con acetato de etilo (60 ml), y la capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (4:1-73:27)] para obtener 2-(2-{[(3R,5S)-1-(3-{[ter-butil(dimetil)silil]-oxi}-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-fenilpropionato de etilo (0.33 g, 0.41 mmoles, 59%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: -0.11 (3H, s), -0.02 (3H, s), 0.85 (3H, s), 0.88 (9H, s), 1.00 (3H, s), 1.15 (3/2H, t, J = 6.9 Hz), 1.16 (3/2H, t, J = 6.9 Hz), 3.05 (1/2H, dd, J = 4.8, 6.9 Hz), 3.10 (1/2H, dd, J = 4.8, 6.9 Hz), 3.19 (1H, d, J = 9.6

Hz), 3.24 (1H, d, J = 9.6 Hz), 3.32 (1/2H, dd, J = 3.3, 8.4 Hz), 3.37 (1/2H, dd, J = 3.3, 8.4 Hz), 3.44 (1H, dd, J = 7.5, 15.0 Hz), 3.53 (1H, dd, J = 5.7, 15.0 Hz), 3.62 (3H, s), 3.68 (1H, d, J = 14.1 Hz), 3.89 (3H, s), 4.02-4.16 (3H, m), 4.25-4.34 (1H, m), 4.41 (1H, d, J = 14.1 Hz), 6.28 (1H, s), 6.57 (1H, s), 6.92-7.00 (1H, m), 7.08-7.33 (9H, m), 7.37 (1H, s).

(3) Un complejo de trifluoruro de boro-éter dietílico (0.16 ml, 1.22 mmoles) se añadió gota a gota a una solución de 2-(2-{[(3R,5S)-1-(3-{[ter-butil(dimetil)silil]-oxi}-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-fenilpropionato de etilo (0.33 g, 0.41 mmoles) obtenido en el ejemplo 99-(2) en acetonitrilo (5 ml). Después de agitarse a la misma temperatura durante 1.5 horas, se añadió agua (2 ml) al mismo y la mezcla se extrajo con acetato de etilo (60 ml). La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (1:1-2:3)] para obtener 2-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-fenilpropionato de etilo (0.24 g, 0.35 mmoles, 85%) como polvo no cristalino incoloro.

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^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.06 (3H, s), 1.16 (3H, t, J = 7.2 Hz), 3.00-3.21 (2H, m), 3.29-3.50 (3H, m), 3.55 (1H, dd, J = 5.7, 15.3 Hz), 3.59-3.70 (1H, m), 3.62 (3H, s), 3.89 (3H, s), 4.00-4.21 (4H, m), 4.27-4.39 (1H, m), 4.49 (1H, d, J = 14.4 Hz), 6.20 (1H, s), 6.57 (1H, d, J c 1.5 Hz), 6.94-7.01 (1H, m), 7.03-7.35 (9H, m), 7.37 (1H, s).

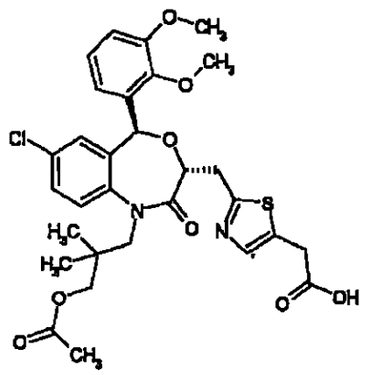
(4) Una mezcla de 2-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-fenilpropionato de etilo (0.2 g, 0.29 mmoles) obtenido en el ejemplo 99-(3), una solución acuosa 1 N de hidróxido de sodio (1 ml) y etanol (5 ml) se agitó a temperatura ambiente durante 1 hora. La mezcla se acidificó con ácido clorhídrico acuoso 1 N (2.3 ml) y después se extrajo con acetato de etilo (35 ml). La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener ácido 2-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-fenilpropiónico (0.19 g, 0.29 mmoles, cuant.) como un polvo no cristalino incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.04 (3/2H; s), 1.05 (3/2H, s), 3.06 (1H, dd, J = 7.5, 13.8 Hz), 3.18 (1H, d, J =

12.0 Hz), 3.37 (1H, d, J = 14.7 Hz), 3.30-3.63 (3H, m), 3.61 (3H, s), 3.63 (1H, d, J = 12.0 Hz), 3.87 (3/2H, s), 3.88 (3/2H, s), 4.05-4.17 (1H, m), 4.27-4.37 (1H, m), 4.46 (1H, d, J= 14.7 Hz), 6.19 (1H, s), 6.55-6.60 (1H, m), 6.92-7.00 (1H, m), 7.05-7.41 (10H, m).

EJEMPLO 100

Acido (2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acético



De conformidad con una manera similar a la del ejemplo 14, se obtuvo el compuesto del título.

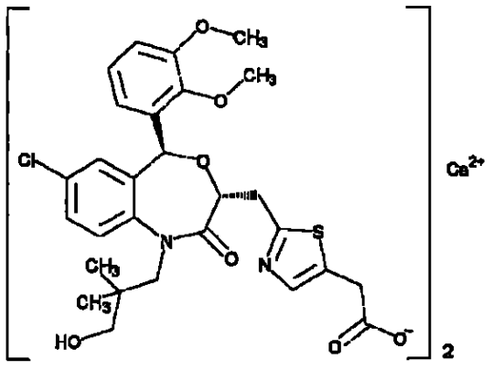
^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 2.02 (3H, s), 3.39-3.62 (3H, m), 3.61 (3H, s), 3.73 (1H, d, J = 10.8 Hz), 3.82 (2H, s), 3.85 (1H, d, J = 10.8 Hz), 3.88 (3H, s), 4.33 (1H, t, J = 6.9 Hz), 4.56 (1H, d, J = 13.8 Hz), 6.30 (1H, s), 6.59 (1H, d, J = 2.4 Hz), 6.96 (1H, dd, J = 3.3, 6.6

Hz), 7.10-7.20 (2H, m), 7.26-7.34 (2H, m), 7.47 (1H, s).

EJEMPLO 101

Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acético

Sal de calcio



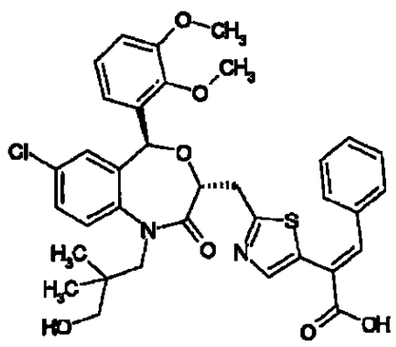
De conformidad con una manera similar a la del ejemplo 27, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.61 (3H, s), 0.87 (3H, s), 3.04-3.30 (3H, m), 3.40-3.65 (7H, m), 3.84 (3H, s), 4.23-4.50 (2H, m), 6.13 (1H, s), 6.55 (1H, s), 6.93 (1H, d, J = 8.1 Hz), 7.09-7.38 (5H, m).

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EJEMPLO 102

Acido (2Z)-2-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-fenilacrílico



(1) Bistrimetilsililamida de litio (1.33 ml, 1.46 mmoles) se añadió gota a gota a una solución de (2-{[(3R,5S)-1-(3-{[ter-butil(dimetil)silil]oxi}-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acetato de etilo (1.0 g, 1.39 mmoles) obtenido en el ejemplo 99-(1) en THF (10 ml) a -78°C bajo atmósfera de nitrógeno. Después de agitarse a la misma temperatura durante 1 hora, se añadió gota a gota benzaldehido (0.15 g, 1.39 mmoles) a la misma y la mezcla se agitó a -20°C durante 5 horas. Después de que se añadió una solución acuosa saturada de cloruro de amonio (5 ml), la mezcla se extrajo con acetato de etilo (120 ml) y la capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio y después se

concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (73:27-62:38)] para obtener 2-(2-{[(3R,5S)-1-(3-{[ter-butil (dimetil)silil]-oxi}-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-hidroxi-3-fenilpropionato de etilo (0.23 g, 0.28 mmoles, 20%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: -0.11 (3H, s), -0.02 (3H, s), 0.80-1.35 (9H, m), 0.87 (9H, s), 2.90-3.28 (3H, m), 3.30-3.74 (6H, m), 3.88 (3H, s), 4.00-4.43 (4H, m), 5.03-5.12 (1/2H, m), 5.17 (1/2H, m), 6.25 (1/2H, s), 6.27 (1/2H, s), 6.56 (1H, br), 6.90-7.40 (11H, m).

(2) Trietilamina (0.06 ml, 0.43 mmoles) y cloruro de metansulfonilo (0.03 ml, 0.43 mmoles) se añadieron a una solución de 2-(2-{[(3R,5S)-1-(3-{[ter-butil(dimetil)silil]-oxi}-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-hidroxi-3-fenilpropionato de etilo (0.22 g, 0.27 mmoles) obtenido en el ejemplo 102-(1) en THF (5 ml) bajo enfriamiento con hielo. Después de agitarse a la misma temperatura durante 1.5 horas, DBU (0.08 ml, 0.53 mmoles) se añadió gota a gota a la misma y la mezcla se agitó durante 2 horas. Después de que se añadió agua (5 ml), la solución de

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reacción se extrajo con acetato de etilo (60 ml) y la capa orgánica se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (67:33-1:1)] para obtener (2Z)-2-(2-{[(3R,5S)-1-(3-{[ter-butil(dimetil)silil]oxi}-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-fenilacrilato de etilo (0.09 g, 0.12 mmoles, 44%) como polvo no cristalino incoloro.

^{1}H-RMN ($CDCl_3$) δ: -0.10 (3H, s), -0.01 (3H, s), 0.85 (3H, s), 0.88 (9H, s), 1.00 (3H, s), 1.33 (3H, t, J = 7.2 Hz), 3.20 (1H, d, J = 9.9 Hz), 3.24 (1H, d, J = 9.9 Hz), 3.50-3.59 (2H, m), 3.62 (3H, s), 3.69 (1H, d, J = 13.8 Hz), 3.88 (3H, s), 4.20-4.35 (3H, m), 4.42 (1H, d, J = 13.8 Hz), 6.29 (1H, s), 6.57 (1H, s), 6.95 (1H, dd, J = 2.4, 7.5 Hz), 6.99-7.11 (2H, m), 7.14-7.37 (4H, m), 7.44 (1H, s), 7.93 (1H, s).

(3) Un complejo de trifluoruro de boro-éter dietílico (22 µl, 0.18 mmoles) se añadió gota a gota a una solución de (2Z)-2-(2-{[(3R,5S)-1-(3-{[ter-butil(dimetil)-silil]oxi}-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-

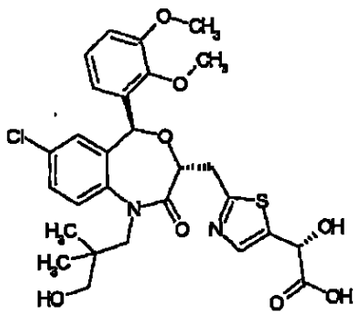
tiazol-5-il)-3-fenilacrilato de etilo (0.09 g, 0.12 mmoles) obtenido en el ejemplo 102-(2) en acetonitrilo (5 ml) bajo enfriamiento con hielo. Después de agitarse a la misma temperatura durante 1.5 horas, se añadió agua (2 ml) a la misma y la mezcla se extrajo con acetato de etilo (60 ml). La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se disolvió en etanol (3 ml), se añadió una solución acuosa 1 N de hidróxido de sodio (0.6 ml), y la mezcla se agitó a temperatura ambiente durante 5 horas. La solución de reacción se acidificó con ácido clorhídrico acuoso 1 N (1 ml) y después se extrajo con acetato de etilo (35 ml). La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener ácido (2Z)-2-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-fenilacrílico (0.07 g, 0.11 mmoles, 85%) como un polvo no cristalino amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.06 (3H, s), 3.18 (1H, d, J = 12.0 Hz), 3.39 (1H, d, J = 14.4 Hz), 3.53-3.69 (3H, m), 3.61 (3H, s), 3.87 (3H, s), 4.37 (1H, dd, J = 5.7,

7.2 Hz), 4.49 (1H, d, J = 14.4 Hz), 6.21 (1H, s), 6.58 (1H, d, J = 1.8 Hz), 6.90-7.00 (1H, m), 7.02-7.10 (2H, m), 7.17-7.40 (7H, m), 7.51 (1H, s), 8.06 (1H, s).

EJEMPLO 103

Acido (2R)-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)(hidroxi)acético

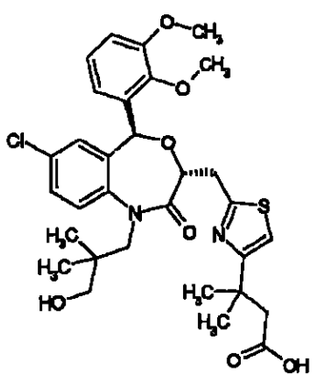


De conformidad con una manera similar a la del ejemplo 99, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.03 (3H, s), 3.20 (1H, d, J = 12.3 Hz), 3.38 (1H, d, J = 14.1 Hz), 3.48 (1H, dd, J = 6.6, 15.3 Hz), 3.53-3.67 (2H, m), 3.60 (3H, s), 3.88 (3H, s), 4.30-4.40 (1H, m), 4.44 (1H, d, J = 14.1 Hz), 5.33 (1H, s), 6.18 (1H, s), 6.59 (1H, d, J= 1.8 Hz), 6.97 (1H, dd, J = 1.8, 7.8 Hz), 7.09-7.21 (2H, m), 7.26-7.40 (2H, m), 7.66 (1H, s).

EJEMPLO 104

Acido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-4-il)-3-metilbutanoico



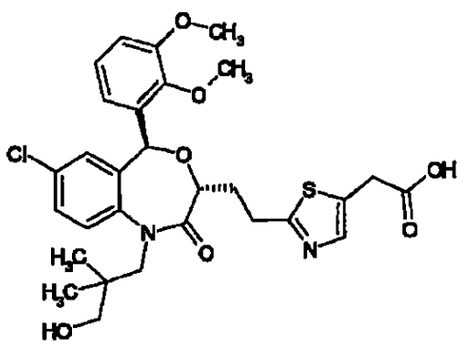
De conformidad con una manera similar a la del ejemplo 16, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 1.39 (3H, s), 1.41 (3H, s), 2.71 (2H, s), 3.10-3.21 (1H, brs), 3.43 (1H, d, J = 14.4 Hz), 3.51 (1H, dd, J = 6.3, 15.6 Hz), 3.59-3.71 (2H, m), 3.62 (3H, s), 3.89 (3H, s), 4.32 (1H, t, J = 6.3 Hz), 4.46 (1H, d, J = 14.4 Hz), 6.21 (1H, s), 6.60 (1H, d, J = 1.8 Hz), 6.92 (1H, s), 6.99 (1H, dd, J = 2.7, 7.5 Hz), 7.10-7.20 (2H, m), 7.35-7.45 (2H, m).

614
623

EJEMPLO 105

Acido (2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,3-tiazol-5-il)acético



(1) A una solución de (3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-etanol (1.0 g, 1.98 mmoles) obtenido en el ejemplo 50-(1), cianohidrina de acetona (0.23 ml, 2.57 mmoles) y tolueno (20 ml) se añadieron n-tributilfosfina (0.74 ml, 2.96 mmoles) y 1,1,-azodicarbonildipiperidina (0.75 g, 2.96 mmoles) bajo atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante 3 horas. Después, se añadió hexano (10 ml), la mezcla se agitó durante 30 minutos y después se filtró para remover sustancias insolubles. El filtrado se concentró bajo presión reducida y el residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (7:3-3:2)] para obtener acetato de 3-[(3R,5S)-7-cloro-3-(2-cianoetil)-5-(2,3-

dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (0.75 g, 1.46 mmoles, 74%) como polvo no cristalino incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 2.03 (3H, s), 2.00-2.35 (2H, m), 2.57 (2H, t, J = 7.5 Hz), 3.53 (1H, d, J = 14.4 Hz), 3.62 (3H, s), 3.72 (1H, d, J = 11.1 Hz), 3.86 (1H, d, J = 11.1 Hz), 3.90 (3H, s), 3.99 (1H, dd, J = 4.8, 7.5 Hz), 4.57 (1H, d, J = 14.4 Hz), 6.27 (1H, s), 6.66 (1H, d, J = 2.1 Hz), 7.00 (1H, dd, J = 3.0, 7.2 Hz), 7.16-7.25 (2H, m), 7.30 (1H, d, J= 8.7 Hz), 7.36 (1H, dd, J= 2.1, 8.7 Hz).

(2) Ditiofosfato de O,O'-dietilo (0.20 ml, 1.17 mmoles) se añadió a una solución de acetato de 3-[(3R,5S)-7-cloro-3-(2-cianoetil)-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (0.5 g, 0.97 mmoles) obtenido en el ejemplo 105-(1) y HCl 4 N (2.5 ml), y la mezcla se agitó a temperatura ambiente durante 16 horas. Después de que se añadió agua (5 ml), la mezcla se extrajo con acetato de etilo y la capa orgánica se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (3:2-1:1)] para obtener acetato de 3-[(3R,5S)-3-(3-amino-3-tioxopropil)-7-cloro-5-

(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (0.38 g, 0.69 mmoles, 71%) como un cristal amarillo pálido.

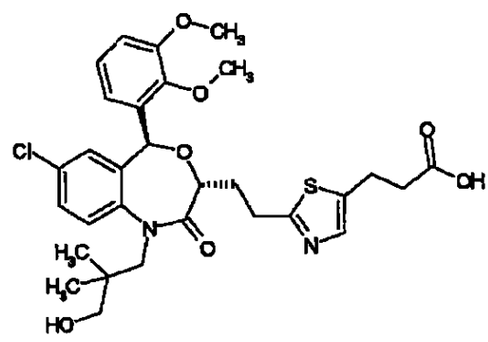
^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.01 (3H, s), 2.03 (3H, s), 2.20-2.34 (2H, m), 2.71-2.94 (2H, m), 3.52 (1H, d, J = 14.1 Hz), 3.62 (3H, s), 3.72 (1H, d, J = 11.1 Hz), 3.88 (1H, d, J = 11.1 Hz), 3.90 (3H, s), 3.96 (1H, t, J = 6.3 Hz), 4.56 (1H, d, J = 14.1 Hz), 6.26 (1H, s), 6.64 (1H, d, J = 2.4 Hz), 6.95-7.04 (1H, m), 7.15-7.24 (2H, m), 7.29 (1H, d, J = 9.0 Hz), 7.35 (1H, dd, J = 2.4, 9.0 Hz), 7.30-7.40 (1H, m), 7.48 (1H , br).

(3) De conformidad con una manera similar a la del ejemplo 16 con el uso acetato de 3-[(3R,5S)-3-(3-amino-3-tioxopropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo obtenido en el ejemplo 105-(2), se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.04 (3H, s), 2.18-2.42 (2H, m), 2.95-3.20 (3H, m), 3.37 (1H, d, J = 14.4 Hz), 3.57-3.70 (1H, m), 3.61 (3H, s), 3.74 (2H, s), 3.82-3.99 (1H, m), 3.89 (3H, s), 4.46 (1H, d, J = 14.4 Hz), 6.15 (1H, s), 6.59 (1H, s), 6.92-7.02 (1H, m), 7.13-7.23 (2H, m), 7.25-7.40 (3H, m).

EJEMPLO 106

Acido 3-(2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,3-tiazol-5-il)propiónico



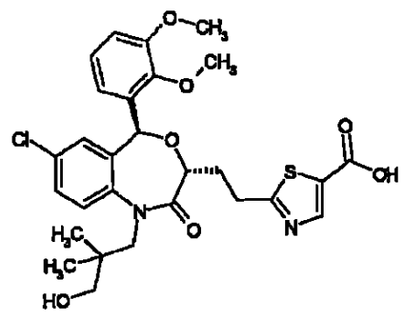
De conformidad con una manera similar a la del ejemplo 105, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.04 (3H, s), 2.17-2.41 (2H, m), 2.62 (2H, t, J = 7.2 Hz), 2.95-3.21 (5H, m), 3.36 (1H, d, J = 14.4 Hz), 3.607 (3H, s), 3.612 (1H, d, J = 11.7 Hz), 3.88 (3H, s), 3.84-3.94 (1H, m), 4.44 (1H, d, J = 14.4 Hz), 6.14 (1H, s), 6.60 (1H, d, J= 1.8 Hz), 6.98 (1H, dd, J = 2.4, 6.9 Hz), 7.13-7.22 (2H, m), 7.26 -7.40 (3H, m).

618
627

EJEMPLO 107

Acido 2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,3-tiazol-5-carboxílico

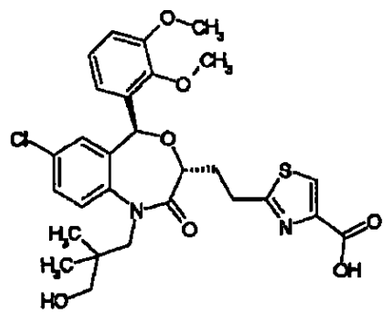


De conformidad con una manera similar a la del ejemplo 105, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.06 (3H, s), 2.20-2.50 (2H, m), 3.08-3.32 (2H, m), 3.17 (1H, d, J = 11.4 Hz), 3.37 (1H, d, J= 14.4 Hz), 3.62 (3H, s), 3.63 (1H, d, J= 11.4 Hz), 3.89 (3H, s), 3.95 (1H, dd, J = 5.1, 7.5 Hz), 4.48 (1H, d, J = 14.4 Hz), 6.16 (1H, s), 6.61 (1H, d, J = 2.1 Hz), 6.99 (1H, dd, J = 3.0, 6.6 Hz), 7.13-7.23 (2H, m), 7.29 (1H, d, J = 8.7 Hz), 7.35 (1H, dd, J = 2.1, 8.7 Hz), 8.27 (1H, s).

EJEMPLO 108

Acido 2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,3-tiazol-4-carboxílico

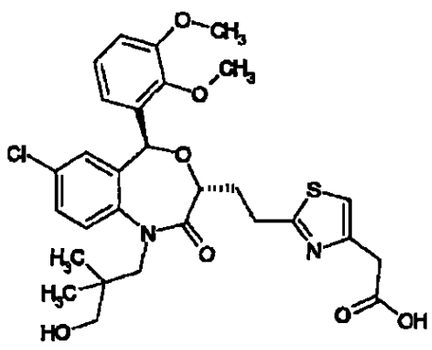


De conformidad con una manera similar a la del ejemplo 105, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.22-2.50 (2H, m), 3.06-3.38 (2H, m), 3.17 (1H, d, J = 11.4 Hz), 3.37 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.62 (1H, d, J = 11.4 Hz), 3.89 (3H, s), 3.95 (1H, dd, J = 5.4, 7.5 Hz), 4.46 (1H, d, J = 14.1 Hz), 6.15 (1H, s), 6.60 (1H, d, J = 2.1 Hz), 6.99 (1H, dd, J = 2.4, 7.5 Hz), 7.10-7.23 (2H, m), 7.31 (1H, d, J = 8.4 Hz), 7.36 (1H, dd, J = 2.1, 8.4 Hz), 8.10 (1H, s).

EJEMPLO 109

Acido (2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,3-tiazol-4-il)acético

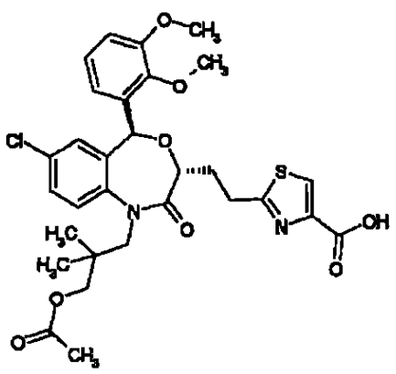


De conformidad con una manera similar a la del ejemplo 105, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.18-2.45 (2H, m), 3.03-3.30 (3H, m), 3.38 (1H, d, J = 14.4 Hz), 3.617 (3H, s), 3.618 (1H, d, J = 11.7 Hz), 3.77 (2H, d, J = 1.2 Hz), 3.89 (3H, s), 3.93 (1H, dd, J = 5.4, 7.5 Hz), 4.47 (1H, d, J = 14.4 Hz), 6.16 (1H, s), 6.61 (1H, d, J = 2.1 Hz), 6.95 (1H, t, J = 1.2 Hz), 6.95-7.01 (1H, m), 7.16-7.23 (2H, m), 7.31 (1H, d, J = 8.4 Hz), 7.36 (1H, dd, J = 2.1, 8.4 Hz).

EJEMPLO 110

Acido 2-{2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,3-tiazol-5-carboxílico

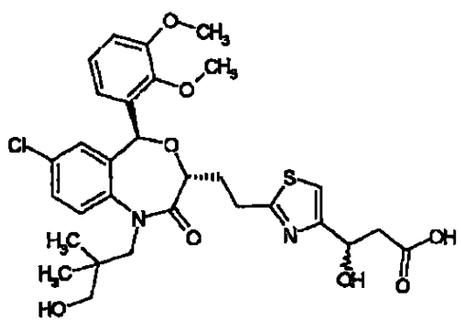


De conformidad con una manera similar a la del ejemplo 14, se obtuvo el compuesto del título.

^{1}H-RMN (CD_3OD) δ: 0.98 (3H, s), 0.99 (3H, s), 1.98 (3H, s), 1.90-2.23 (2H, m), 2.90-3.20 (2H, m), 3.58 (3H, s), 3.60-3.92 (3H, m), 3.87 (3H, s), 4.45 (1H, d, J = 14.1 Hz), 4.75-4.90 (1H, m), 6.20 (1H, s), 6.51 (1H, d, J = 2.1 Hz), 6.99-7.21 (3H, m), 7.35-7.45 (1H, m), 7.54 (1H, d, J = 9.0 Hz), 7.90 (1H, s).

EJEMPLO 111

Acido 3-(2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,3-tiazol-4-il)-3-hidroxipropiónico

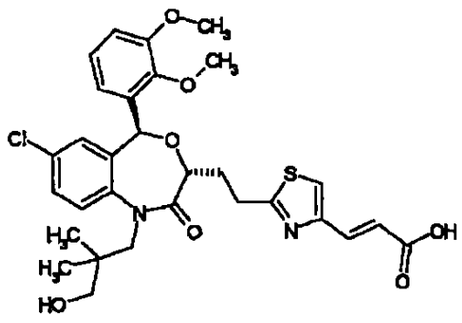


De conformidad con una manera similar a la del ejemplo 18, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.18-2.42 (2H, m), 2.73-2.82 (1H, m), 2.82-2.96 (2H, m), 3.00-3.22 (2H, m), 3.15 (1H, d, J = 12.0 Hz), 3.37 (1H, d, J = 13.8 Hz), 3.61 (3H, s), 3.62 (1H, d, J = 12.0 Hz), 3.89 (3H, s), 3.90-4.01 (1H, m), 4.47 (1H, d, J = 13.8 Hz), 5.10-5.17 (1H, m), 6.15 (1H, s), 6.60 (1H, d, J = 2.1 Hz), 6.95-7.01 (1H, m), 7.07 (1H, s), 7.15-7.21 (2H, m), 7.31 (1H, d, J = 8.7 Hz), 7.36 (1H, dd, J = 2.1, 8.7 Hz).

EJEMPLO 112

Acido (2E)-3-(2-{2-[3R,5S]-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il}etil)-1,3-tiazol-4-il)acrílico

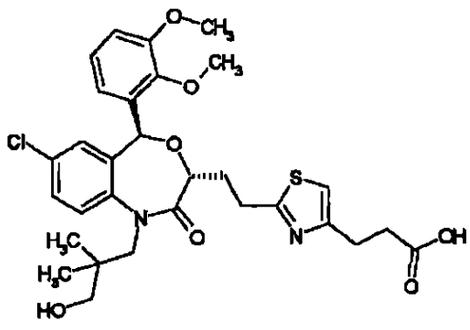


De conformidad con una manera similar a la del ejemplo 19, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.06 (3H, s), 2.20-2.43 (2H, m), 3.05-3.24 (3H, m), 3.38 (1H, d, J = 14.4 Hz), 3.62 (3H, s), 3.60-3.69 (1H, m), 4.05 (1H, dd, J = 5.7, 7.2 Hz), 4.47 (1H, d, J = 14.4 Hz), 6.16 (1H, s), 6.59 (1H, d, J = 15.3 Hz), 6.60 (1H, d, J = 2.4 Hz), 6.98 (1H, dd, J = 2.7, 6.6 Hz), 7.14-7.29 (3H, m), 7.32 (1H, d, J = 8.7 Hz), 7.37 (1H, dd, J = 2.4, 8.4 Hz), 7.58 (1H, d, J = 15.3 Hz).

EJEMPLO 113

Acido 3-(2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,3-tiazol-4-il)propiónico

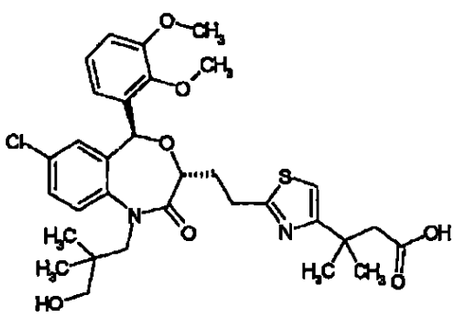


De conformidad con una manera similar a la del ejemplo 88, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.20-2.42 (2H, m), 2.60-2.75 (2H, m), 2.90-3.25 (3H, m), 3.38 (1H, d, J = 14.7 Hz), 3.619 (3H, s), 3.624 (1H, d, J = 11.7 Hz), 3.89 (3H, s), 3.96 (1H, dd, J = 5.4, 6.9 Hz), 4.48 (1H, d, J = 14.7 Hz), 6.16 (1H, s), 6.61 (1H, d, J = 1.8 Hz), 6.80 (1H, s), 6.96-7.03 (1H, m), 7.17-7.23 (2H, m), 7.27-7.40 (2H, m).

EJEMPLO 114

Acido 3-(2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,3-tiazol-4-il)-3-metilbutanoico



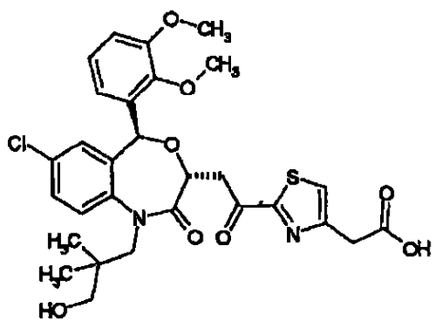
De conformidad con una manera similar a la del ejemplo 16, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.06 (3H, s), 1.38 (3H, s), 1.39 (3H, s), 2.20-2.42 (2H, m), 2.67 (1H, d, J = 15.0 Hz), 3.10-3.35 (3H, m), 3.41 (1H, d, J = 14.7 Hz), 3.62 (3H, s), 3.63 (1H, d, J= 11.7 Hz), 3.90 (3H, s), 3.96 (1H, t, J =5.7 Hz), 4.48 (1H, d, J=14.7 Hz), 6.16 (1H, s), 6.61 (1H, s), 6.90 (1H, s), 7.00 (1H, dd, J = 2.1, 7.8 Hz), 7.14-7.22 (2H, m), 7.30-7.40 (2H, m).

626
625

EJEMPLO 115

Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}-1,3-tiazol-4-il)acético



(1) Una solución de un complejo de trióxido de azufre-piridina (5.76 g, 36.2 mmoles) en DMSO (18 ml) se añadió gota a gota a una solución de (3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-etanol (3.66 g, 7.23 mmoles) obtenida en el ejemplo 50-(1) en diclorometano (70 ml). Después de agitarse a temperatura ambiente durante 1.5 horas, se añadió agua (15 ml). Después de la extracción con diclorometano (150 ml), la capa orgánica se lavó con una solución acuosa al 5% de sulfato ácido de potasio, una solución acuosa de bicarbonato de sodio, agua y una solución acuosa saturada de cloruro de sodio, y después se secó sobre sulfato de magnesio. Después de concentrarse bajo presión reducida, el residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-

acetato de etilo (2:1)] y después se lavó con 2-propanol-hexano para obtener acetato de 3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-3-(2-oxoetil)-2,3-dihidro-4,1-benzoxazepin-1(5H}-il]-2,2-dimetilpropilo (2.39 g, 4.74 mmoles, 66%) como un cristal blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 2.03 (3H, s), 2.86 (1H, ddd, J = 1.2, 5.4, 17.7 Hz), 3.09 (1H, ddd, J = 1.2, 6.9, 17.7 Hz), 3.55 (1H, d, J = 14.4 Hz), 3.62 (3H, s), 3.73 (1H, d, J = 11.1 Hz), 3.86 (1H, d, J = 11.1 Hz), 3.89 (3H, s), 4.42 (1H, dd, J = 5.4, 6.9 Hz), 4.56 (1H, d, J = 14.1 Hz), 6.28 (1H, s), 6.66 (1H, d, J = 1.8 Hz), 6.96-7.01 (1H, m), 7.15-7.23 (2H, m), 7.28-7.40 (2H, m), 9.81 (1H, br).

(2) Una solución de acetato de 3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-3-(2-oxoetil)-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (2.0 g, 3.97 mmoles) obtenido en el ejemplo 115-(1) en diclorometano (25 ml) se añadió gota a gota a una solución de cianuro de ter-butildimetilsililo (0.59 g, 4.17 mmoles), cianuro de potasio (44 mg, 0.68 mmoles) y 18-corona-6-éter (0.42 g, 1.59 mmoles) en dıclorometano (25 ml) bajo atmósfera de nitrógeno. La mezcla se agitó a temperatura ambiente durante 18 horas y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel

de sílice [solvente de revelado: hexano-acetato de etilo (41:9-3:1)] para obtener acetato de 3-[(3R,5S)-3-(2-{[ter-butil(dimetil)silil]oxi}-2-cianoetil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (1.96 g, 3.04 mmoles, 77%) como un cristal blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.04 (3H. s), 0.14 (3/2H, s), 0.15 (3/2H, s), 0.68 (9/2H, s), 0.79 (9/2H, s), 0.95 (3/2H, s), 0.96 (3/2H, 5), 2.03 (3H, s), 2.18-2.45 (2H, m), 3.52 (1H, d, J = 14.1 Hz), 3.62 (3H, s), 3.73 (1/2H, d, J = 11.1 Hz), 3.74 (1/2H, d, J = 11.1 Hz), 3.98-4.16 (1H, m), 4.55 (1/2H, d, J = 14.1 Hz), 4.56 (1/2H, d, J = 14.1 Hz), 4.61-4.76 (1H, m), 6.26 (1H, s), 6.99 (1/2H, d, J = 2.7 Hz), 7.01 (1/2H, d, J = 2.7 Hz), 6.95-7.02 (1H, m), 7.10-7.39 (4H, m).

(3) Acido difenilditiofosfórico (0.39 g, 1.55 mmoles) se añadió a una solución de acetato de 3-[(3R,5S)-3-(2-{[ter-butil(dimetil)silil]oxi}-2-cianoetil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (0.5 g, 0.78 mmoles) obtenido en el ejemplo 115-(2) en alcohol isopropílico (10 ml), y la mezcla se agitó a 60°C durante 14 horas. La mezcla se enfrió a temperatura ambiente y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-

acetato de etilo (41:9-3:1)] para obtener acetato de 3-[(3R,5S)-3-(3-amino-2-{[ter-butil(dimetil)silil]oxi}-3-tioxopropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (0.48 g, 0.71 mmoles, 91%) como un cristal blanco.

^{1}H-RMN ($CDCl_3$) δ: -0.06 (3/2H, s), -0.02 (3/2H, s), 0.03 (3/2H, s), 0.04 (3/2H, s), 0.76 (9/2H, s), 0.81 (9/2H, s), 0.94 (3/2H, s), 0.95 (3/2H, s), 1.03 (3H, s), 2.03 (3H, s), 2.01-2.20 (1H, m), 2.39-2.60 (1H, m), 3.51 (1/2H, d, J = 14.1 Hz), 3.52 (1/2H, d, J = 14.1 Hz), 3.60 (3H, s), 3.69-3.78 (1H, m), 3.84 (1/2H, d, J = 10.8 Hz), 3.85 (1/2H, d, J = 10.8 Hz), 3.89 (3H, s), 4.08 (1/2H, dd, J= 6.0, 10.5 Hz), 4.29 (1/2H, t, J = 6.6Hz), 4.54 (1/2H, d, J = 14.1 Hz), 4.56 (1/2H, d, J = 14.1 Hz), 4.63 (1/2H, t, J = 6.6 Hz), 4.72 (1/2H, dd, J = 4.5, 9.0 Hz), 6.25 (1H, s), 6.60-6.67 (1H, m), 6.95-7.01 (1H, m), 7.14-7.43 (5H, m), 7.72-7.82 (1H, m).

(4) Una solución de acetato de 3-[(3R,5S)-3-(3-amino-2-{[ter-butil(dimetil)silil]oxi}-3-tioxopropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (0.42 g, 0.62 mmoles) obtenido en el ejemplo 115-(3) y 4-cloro-3-oxobutanoato de etilo (84 µl, 0.62 mmoles) en etanol (10 ml) se agitó a 80°C durante 32 horas. Después de reposar hasta enfriarse, se añadió agua (5 ml) a la misma y la mezcla se

extrajo con acetato de etilo (130 ml). La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (41:9-3:1)] para obtener (2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-(1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-1-hidroxietil}-1,3-tiazol-4-il)acetato de etilo (0.18 g, 0.28 mmoles, 45%) como un cristal blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 1.26 (3H, t, J = 7.2 Hz), 2.25-2.48 (1H, m), 2.50-2.70 (1H, m), 3.15 (1H, t, J = 11.1 Hz), 3.38 (1H, d, J = 14.4 Hz), 3.54-3.70 (1H, m), 3.62 (3/2H, s), 3.64 (3/2H, s), 3.74 (1H, s), 3.75 (1H, s), 3.89 (3H, s), 3.99 (1/2H, dd, J = 4.2, 11.1 Hz), 4.07 (1/2H, dd, J = 4.2, 11.1 Hz), 4.10-4.30 (3H, m), 4.47 (1/2H, d, J = 14.4 Hz), 4.50 (1/2H, d, J = 14.4 Hz), 5.11-5.23 (1H, m), 6.18 (1/2H, s), 6.19 (1/2H, s), 6.61 (1/2H, d, J = 2.1 Hz), 6.63 (1/2H, d, J = 2.1 Hz), 6.94-7.02 (1H, m), 7.095 (1/2H, s), 7.103 (1/2H, s), 7.14-7.40 (4H, m).

(5) Dióxido de manganeso (0.2 g, 2.38 mmoles) se añadió a una solución de (2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-1-hidroxietil}-1,3-tiazol-

4-il)acetato de etilo (0.15 g, 0.24 mmoles) obtenido en el ejemplo 115-(4) en THF (5 ml), y la mezcla se agitó a 70°C durante 4 días. Después de reposar hasta enfriarse, se filtraron sustancias insolubles con el uso de Celite y el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (3:1-2:1)] para obtener (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}-1,3-tiazol-4-il)acetato de etilo (71 mg, 0.11 mmoles, 48%) como un cristal blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 1.29 (3H, t, J = 6.9 Hz), 3.14 (1H, t, J = 10.5 Hz), 3.41 (1H, d, J = 14.4 Hz), 3.58 (1H, dd, J = 4.8, 18.3 Hz), 3.56-3.69 (1H, m), 3.62 (3H, s), 3.89 (3H, s),3.98 (1H, dd, J = 8.1, 18.3 Hz), 4.15 (1H, dd, J = 3.9, 10.8 Hz), 4.20 (2H, q, J = 6.9 Hz), 4.49 (1H, d, J = 14.4 Hz), 4.60 (1H, dd, J = 4.8, 8.1 Hz), 6.18 (1H, s), 6.63 (1H, s), 6.95-7.01 (1H, m), 7.15-7.22 (2H, m), 7.36-7.43 (2H, m), 7.57 (1H, s).

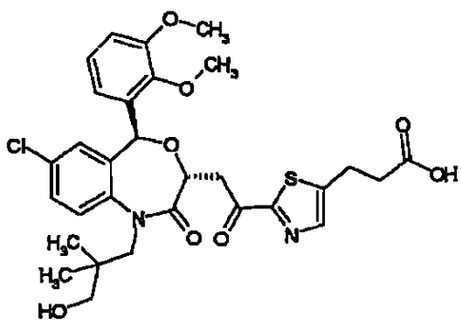
(6) Una solución de (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}-1,3-tiazol-4-il)acetato de etilo (60 mg, 0.10 mmoles) obtenido en el

ejemplo 115-(5) y carbonato de potasio (26 mg, 0.20 mmoles) en etanol (3 ml) y agua (0.5 ml) se calentó a reflujo durante 5 horas con agitación. Después de reposar hasta enfriarse, la mezcla se acidificó con ácido clorhídrico acuoso 1 N (1 ml.) y se extrajo con acetato de etilo (70 ml). La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El cristal resultante se lavó con acetato de etilo-hexano y después se secó bajo presión reducida para obtener ácido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}-1,3-tiazol-4-il) acético (40 mg, 0.07 mmoles, 70%) como un cristal amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 3.16 (1H, d, J = 12.0 Hz), 3.41 (1H, d, J = 14.1 Hz), 3.54 (1H, dd, J = 4.8, 18.3 Hz), 3.61 (3H, s), 3.62 (1H, d, J = 12.0 Hz), 3.88 (3H, s), 3.99 (1H, dd, J = 8.4, 18.3 Hz), 4.47 (1H, d, J = 14.1 Hz), 4.60 (1H, dd, J = 4.8, 8.4 Hz), 6.16 (1H, s), 6.62 (1H, d, J = 2.7 Hz), 6.93-7.00 (1H, m), 7.10-7.20 (2H, m), 7.33-7.42 (2H, m), 7.55 (1H, s).

EJEMPLO 116

Acido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}-1,3-tiazol-5-il)propiónico



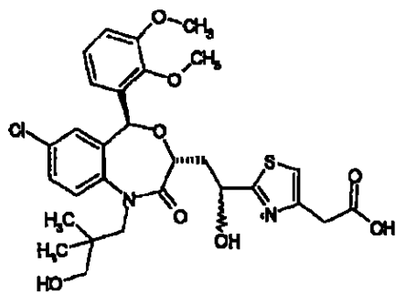
De conformidad con una manera similar a la del ejemplo 115, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 2.76 (2H, t, J = 7.2 Hz), 3.14 (1H, d, J = 12.0 Hz), 3.23 (1H, t, J = 7.2 Hz), 3.41 (1H, d, J = 15.0 Hz), 3.54 (1H, dd, J = 4.8, 18.0 Hz), 3.61 (3H, s), 3.62 (1H, d, J = 12.0 Hz), 3.89 (3H, s), 3.95 (1H, dd, J = 8.4, 18.0 Hz), 4.48 (1H, d, J = 15.0 Hz), 4.58 (1H, dd, J = 4.8, 8.4 Hz), 6.17 (1H, s), 6.62 (1H, s), 6.95-7.01 (1H, m), 7.13-7.20 (2H, m), 7.38-7.42 (2H, m), 7.74 (1H, s).

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EJEMPLO 117

Acido (2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-1-hidroxietil}-1,3-tiazol-4-il)acético



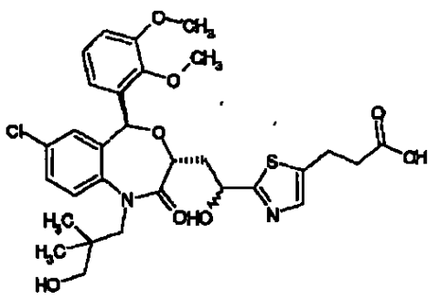
Una mezcla de (2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-1-hidroxietil}-1,3-tiazol-4-il)acetato de etilo (0.25 g, 0.40 mmoles) obtenido en el ejemplo 115-(4), una solución acuosa 1 N de hidróxido de sodio (1 ml) y etanol (5 ml) se agitó a temperatura ambiente durante 2 horas. Esta mezcla se acidificó con ácido clorhídrico acuoso 1 N (1.2 ml) y después se extrajo con acetato de etilo (35 ml). Este extracto se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener ácido (2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-1-hidroxietil}-1,3-tiazol-4-il)acético (0.24 g, 0.40 mmoles, cuant.) como polvo no

cristalino incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.66 (3H, s), 1.05 (3H, s), 2.30-2.70 (2H, m), 3.17 (1H, t, J = 11.7 Hz), 3.40 (1H, d, J = 14.4 Hz), 3.61 (1H, d, J = 11.7 Hz), 3.63 (3H, s), 3.79 (2H, s), 3.90 (3H, s), 4.19-4.32 (1H, m), 4.48 (1/3H, d, J = 14.4 Hz), 4.50 (2/3H, d, J = 14.4 Hz), 5.20-5.30 (1H, m), 6.18 (2/3H, s), 6.21 (1/3H, s), 6.62 (2/3H, d, J = 2.4 Hz), 6.67 (1/3H, d, J = 2.4 Hz), 6.98-7.03 (1H, m), 7.07 (1H, s), 7.15-7.23 (2H, m), 7.30-7.42 (2H, m).

EJEMPLO 118

Acido 3-(2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-1-hidroxietil}-1,3-tiazol-5-il)propiónico



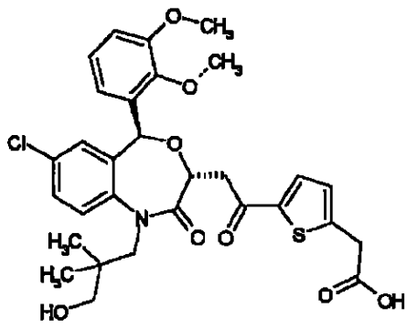
De conformidad con una manera similar a la del ejemplo 117, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.66 (3H, s), 1.04 (3H, s), 2.13-2.41 (2H, m), 2.50-2.60 (1H, m), 2.61 (2H, t, J = 7.5 Hz),

3.10 (2H, t, J = 7.5 Hz), 3.10-3.10 (1H, m), 3.39 (1/2H, d, J = 13.8 Hz), 3.40 (1/2H, d, J = 13.8 Hz), 3.57-3.64 (1H, m), 3.62 (3H, s), 3.90 (3H, 5),4.19-4.30 (1H, m), 4.466 (1/2H, d, J = 13.8 Hz), 4.474 (1/2H, d, J = 13.8 Hz), 5.01-5.20 (1H, m), 6.17 (1/2H, s), 6.19 (1/2H, s), 6.58-6.63 (1H, m), 6.95-7.02 (1H, m), 7.15-7.30 (2H, m), 7.31-7.43 (3H, m).

EJEMPLO 119

Acido (5-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepın-3-il]acetil}-2-tienil)acético



DMF (1 gota) y cloruro de tionilo (0.42 ml, 5.77 mmoles) se añadieron gota a gota a una solución de ácido 2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acético (2.5 g, 4.81 mmoles) en THF (25 ml) a temperatura ambiente. La mezcla se agitó durante 4 horas y después se concentró bajo presión reducida. El residuo resultante se disolvió en diclorometano (30 ml). 2-tiofenoacetato de etilo

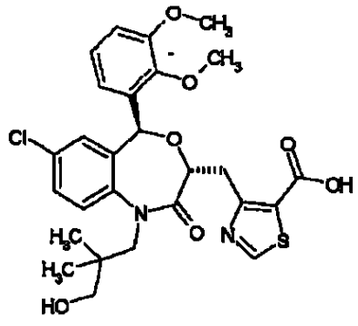
(0.69 ml, 4.57 mmoles) y cloruro de estaño (1.24 ml, 10.6 mmoles) se añadieron gota a gota bajo enfriamiento con hielo a la misma. La mezcla se calentó a temperatura ambiente y se agitó durante 13 horas. La solución de reacción se vació en agua con hielo y se extrajo con diclorometano (170 ml). La capa orgánica se lavó con ácido clorhídrico acuoso 1 N, agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se sometió a cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (1:1-3:7)] para obtener (5-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}-2-tienil)acetato de etilo como una mezcla con impurezas. Esta mezcla se disolvió en etanol (7 ml) y agua (1 ml), se añadió carbonato de potasio (86 mg, 0.63 mmoles) a la misma, y la mezcla se calentó después a reflujo durante 2 horas con agitación. Después de reposar hasta enfriarse, la mezcla se acidificó con ácido clorhídrico acuoso 1 N (1.5 ml) y después se extrajo con acetato de etilo (35 ml). La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía de líquidos preparativa [solvente de revelado: agua-acetonitrilo (9:1-5:95)] para obtener ácido

(5-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}-2-tienil)acético (52 mg, 0.09 mmoles, 2% (2 pasos)) como un polvo no cristalino amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 3.19 (1H, d, J = 11.7 Hz), 3.28 (1H, dd, J = 4.5, 16.8 Hz), 3.41 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.64 (1H, d, J = 11.7 Hz), 3.70 (1H, dd, J = 8.1, 16.8 Hz), 3.89 (5H, s), 4.45 (1H, d, J = 14.1 Hz), 4.58 (1H, dd, J = 4.5, 8.1 Hz), 6.17 (1H, s), 6.62 (1H, s), 6.95-7.10 (2H, m), 7.11-7.20 (2H, m), 7.35-7.41 (2H, m), 7.66 (1H, d, J = 3.6 Hz).

EJEMPLO 120

Acido 4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-carboxílico

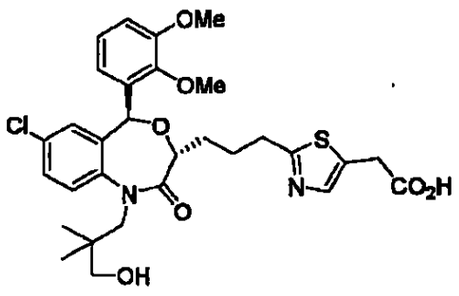


De conformidad con una manera similar a la del ejemplo 26, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 3.15 (1H, d, J = 12.0 Hz), 3.40 (1H, d, J = 14.4 Hz), 3.60 (3H, s), 3.65 (1H, d, J = 12.0 Hz), 3.75 (2H, dd, J = 1.5, 6.6 Hz), 3.88 (3H, s), 4.48 (1H, d, J = 14.4 Hz), 4.55 (1H, t, J = 6.6 Hz), 6.18 (1H , s), 6.55 (1H , s), 6.96 (2H , dd, J = 2.7, 7.8 Hz), 7.13 (1H, t, J = 7.8 Hz), 7.32-7.40 (2H, m), 8.71 (1H, s).

EJEMPLO 121

Acido (2-{3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]propil}-1,3-tiazol-5-il)acético



(1) (Dietoxifosforil)acetato de etilo (4.76 ml, 24 mmoles) se añadió gota a gota a una suspensión de hidruro de sodio (0,88 g, 22 mmoles) en THF (108 ml) a 0°C. Después de agitarse durante 30 minutos, se añadió acetato de 3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-3-(2-oxoetil)-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (10.8

g, 20 mmoles). Después de agitarse durante 1 hora, la mezcla se diluyó con acetato de etilo, se lavó con una solución acuosa saturada de cloruro de amonio y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener (2E)-4-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-2-butenoato de etilo (11.5 g, 20 mmoles, 100%).

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s) 1.03 (3H, s) 1.28 (3H, t, J = 7.06 Hz) 2.03 (3H, s) 2.74 (2H, m) 3.53 (1H, d, J = 14.13 Hz) 3.62 (3H, s) 3.86 (6H, m) 4.18 (2H, q, J = 7.16 Hz) 4.56 (1H, d, J = 14.13 Hz) 5.90 (1H, d, J = 15.64 Hz) 6.26 (1H, s) 6.64 (1H, m, J = 2.26 Hz) 6.95 (2H, m) 7.27 (4H, m).

(2) (2E)-4-[(3R,5S)-1-(3-acetoxi-2,2-dimetil-propil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-2-butenoato de etilo (15 g, 26.1 mmoles) obtenido en el ejemplo 121-(1) se disolvió en metanol (150 ml), se añadió magnesio (3.17 g, 131 mmoles) a la misma, y la mezcla se agitó durante 3 horas. La solución de reacción se diluyó con acetato de etilo, se lavó con ácido clorhídrico acuoso 1 N, una solución acuosa saturada de

cloruro de sodio, se secó sobre sulfato de magnesio anhidro, y después se concentró bajo presión reducida. El residuo se disolvió en metanol (150 ml), se añadió una solución acuosa 1 N de hidróxido de sodio (52 ml) y la mezcla se agitó durante 2 horas. La solución de reacción se concentró bajo presión reducida, y el residuo se disolvió en agua y se lavó con éter. La capa acuosa se acidificó con ácido clorhídrico acuoso 1 N y después se extrajo con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se disolvió en cloruro de metileno (100 ml), se añadieron piridina (6.46 ml, 80 mmoles) y cloruro de acetilo (4.98 ml, 70 mmoles) al mismo, y la mezcla se agitó durante 1 hora. Después se añadió agua (50 ml), la solución de reacción se agitó durante 4 horas y después se extrajo con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener ácido 4-[(3R,5S)-1-[3-acetoxi-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]butanoico (10.9 g, 19.8 mmoles, 76%).

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s) 1.02 (3H, s) 1.56-

2.00 (4H, m) 2.03 (3H, s) 2.37 (2H, t, J = 7.16 Hz) 3.51 (1H, d, J = 14.13 Hz) 3.61 (3H, s) 3.70-3.92 (6H, m) 4.56 (1H, d, J = 14.13 Hz) 6.24 (1H, s) 6.63 (1H, d, J = 2.26 Hz) 6.98 (1H, s dd, J = 7.54, 2.26 Hz) 7.15-7.37 (4H, m).

(3) Se añadió cloruro de carbonato de isobutilo (0.55 ml, 4.20 mmoles) a una solución de ácido 4-[(3R,5S)-1-[3-acetoxi-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]butanoico (2.0 g, 3.65 mmoles) obtenido en el ejemplo 121-(2) y trietilamina (0.53 ml, 3.83 mmoles) en dimetilacetamida (20 ml) a 0°C, y la mezcla se agitó a 0°C durante 30 minutos. A la solución de reacción a 0°C, se añadió clorhidrato de ácido 4-amino-3-oxobutanoico (0.71 g, 4.02 mmoles) obtenido en el ejemplo 1-(2) y después se añadió gota a gota piridina (0.47 ml, 5.84 mmoles).

Después de agitarse a temperatura ambiente durante 1 hora, la solución de reacción se diluyó con acetato de etilo. Esta se lavó con ácido clorhídrico acuoso 1 N, una solución acuosa al 5% de sulfato ácido de potasio, una solución acuosa de bicarbonato de sodio y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se disolvió en THF (20 ml), se añadió reactivo de Lawesson (1.8 g, 4.44 mmoles) al mismo, y la mezcla se agitó a 70°C durante 1 hora. La solución de reacción se diluyó con

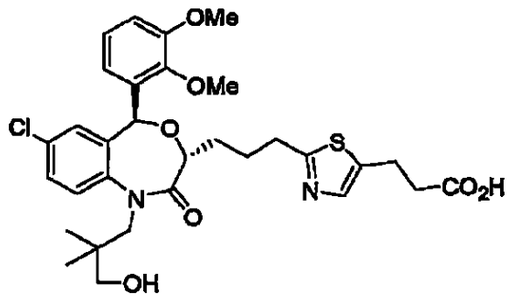
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acetato de etilo, se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se disolvió en etanol (20 ml), se añadió una solución acuosa 1 N de hidróxido de sodio (10 ml), y la mezcla se agitó durante 4 horas. La capa acuosa se acidificó con una solución acuosa al 5% de sulfato ácido de potasio y después se extrajo con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener el compuesto del título (1.0 g, 1.66 mmoles, 43%).

^{1}H-RMN (DMSO-d_6) δ: 0.76 (3H, s) 0.83 {3 H, s) 1.63-1.86 (4H, m) 2.90 (2H, t, J = 6.78 Hz) 3.02-3.20 (2H, m) 3.51 (3H, s) 3.64 (1H, d, J = 14.13 Hz) 3.78-3.87 (m, 5 H) 4.31 (1H, d, J = 14.13 Hz) 4.53 (1H, t, J = 5.09 Hz) 6.05 (1H, s) 6.38 (1H, d, J = 2.45 Hz) 7.15 (2H, d, J = 7.91 Hz) 7.21-7.28 (1H, m) 7.41 (1H, s) 7.51 (1H, dd, J = 8.76, 2.54 Hz,) 7.66 (1H, d, J = 8.85 Hz).

EJEMPLO 122

Acido 3-(2-{3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]propil}-1,3-tiazol-5-il)propiónico

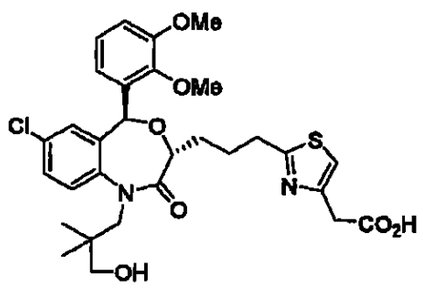


De conformidad con una manera similar a la del ejemplo 121, se obtuvo el compuesto del título.

^{1}H-RMN (DMSO-d_6) δ: 0.75 (3H, s) 0.83 (3H, s) 1.59-1.88 (4H, m) 2.48-2.59 (2H, m) 2.83-3.20 (6H, m) 3.51 (3H, s) 3.64 (1H, d, J = 14.13 Hz) 3.78-3.86 (4H, m) 4.31 (1H, d, J = 14.13 Hz) 4.53 (1H, t, J = 5.09 Hz) 6.05 (1H, s) 6.37 (1H, d, J = 2.45 Hz) 7.11-7.28 (m, 3 H) 7.51 (1H, dd, J = 8.67, 2.45 Hz) 7.66 (1H, d, J = 8.85 Hz).

EJEMPLO 123

Acido (2-{3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepina-3-il]propil}-1,3-tiazol-4-il)acético



(1) Se añadió gota a gota cianometilfosfonato de dietilo (3.88 ml, 24 mmoles) a una suspensión de hidruro de sodio (0.88 g, 22 mmoles) en THF (108 ml) a 0°C. Después de agitarse durante 30 minutos, se añadió acetato de 3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-3-(2-oxoetil)-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (10.8 g, 20 mmoles). Después de agitarse durante 1 hora, la mezcla se diluyó con acetato de etilo, se lavó con cloruro de amonio saturado y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se disolvió en metanol (105 ml), se añadió magnesio (2.4 g, 100 mmoles) y la mezcla se agitó durante 2 horas. La solución de reacción se diluyó con acetato de etilo, se lavó con ácido clorhídrido acuoso 1 N y una solución acuosa saturada de cloruro de sodio, se secó

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sobre sulfato de magnesio anhidro, y después se concentró bajo presión reducida. El residuo se disolvió en cloruro de metileno (68 ml), se añadieron trietilamina (3.69 ml, 26.6 mmoles) y cloruro de acetilo (1.51 ml, 21.2 mmoles) y la mezcla se agitó durante 2 horas. La solución de reacción se diluyó con acetato de etilo, se lavó con una solución acuosa de bicarbonato de sodio y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener acetato de 3-[(3R,5S)-7-cloro-3-(3-cianopropil)-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (5.5 g, 10.4 mmoles, 52%).

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s) 1.02 (3H, s) 1.66-2.41 (9 H, m) 3.47-3.93 (10 H, m) 4.56 (1H, d, J = 14.13 Hz) 6.25 (1H, s) 6.64 (1H, d, J = 2.26 Hz) 6.99 (1H, dd, J = 7.25, 2.35 Hz) 7.14-7.39 (4H, m).

(2) acetato de 3-[(3R,5S)-7-cloro-3-(3-cianopropil)-5-{2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (5.3 g, 10 mmoles) obtenido en el ejemplo 123-(1) se disolvió en una solución de ácido clorhídrico 4 N-acetato de etilo (53 ml). Se añadió ditiofosfato ácido de O,O'-dietilo a la misma (2.01 ml, 12 mmoles) y la mezcla se agitó durante la noche. La solución de

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reacción se lavó con agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener acetato de 2-[(3R,5S)-3-(4-amino-4-tioxobutil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-1,1-dimetiletilo (2.8 g, 4.97 mmoles, 50%).

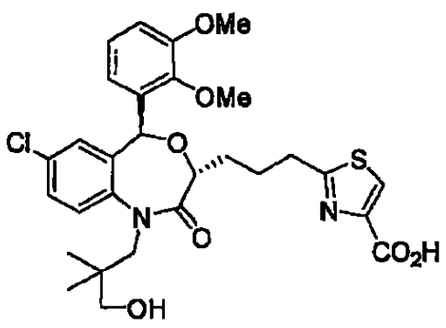
EM (ES+) [M+1] 563

(3) Acetato de 2-[(3R,5S)-3-(4-amino-4-tioxobutil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-1,1-dimetiletilo (0.563 g, 1.0 mmoles) obtenido en el ejemplo 123-(2) se disolvió en etanol (10 ml). Se añadió 4-cloro-3-oxobutanoato de etilo al mismo (0.243 ml, 1.8 mmoles) y la mezcla se agitó a 90°C durante 2 horas. Después de que la solución de reacción se enfrió a temperatura ambiente, una solución acuosa 1 N de hidróxido de sodio (5 ml) se añadió a la misma y la mezcla se agitó durante 5 horas. La capa acuosa se acidificó con sulfato ácido de potasio acuoso al 5% y después se extrajo con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener el compuesto del título (0.3 g, 0.498 mmoles, 50%).

^{1}H-RMN (DMSO-d_6) δ: 0.76 (3H, s) 0.83 (3H, s) 1.63-1.86 (4H, m) 2.90 (2H, t, J = 6.78 Hz,) 3.02-3.20 (2H, m) 3.51 (3H, s) 3.64 (1H, d, J = 14.13 Hz) 3.78-3.87 (5 H, m) 4.31 (1H, d, J = 14.13 Hz) 4.53 (1H, t, J = 5.09 Hz) 6.05 (1H, s) 6.38 (1H, d, J = 2.45 Hz) 7.15 (2H, d, J = 7.91 Hz) 7.21-7.28 (1H, m) 7.41 (1H, s) 7.51 (1H, dd, J = 8.76, 2.54 Hz) 7.66 (1H, d, J = 8.85 Hz).

EJEMPLO 124

Acido 2-{3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]propil}-1,3-tiazol-4-carboxílico



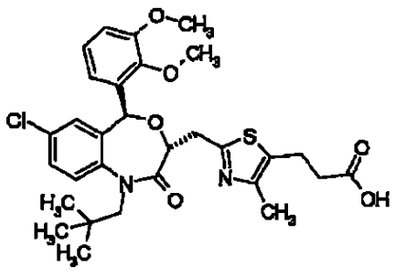
De conformidad con una manera similar a la del ejemplo 123, se obtuvo el compuesto del título.

^{1}H-RMN (DMSO-d_6) δ: 0.75 (3H, s) 0.83 (3H, s) 1.67-1.89 (4H, m) 2.94-3.19 (4H, m) 3.51 (3H, s) 3.64 (1H, d, J = 13.94 Hz) 3.78-3.88 (4H, m) 4.31 (1H, d, J = 14.13 Hz) 4.52 (1H, t, J = 5.27 Hz) 6.05 (1H, s) 6.37 (1H, d, J = 2.45 Hz)

7.12-7.28 (3H, m) 7.50 (1H, dd, J = 8.76, 2.54 Hz,) 7.66 (1H, d, J = 8.85 Hz).

EJEMPLO 125

Acido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxıfenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahıdro-4,1-benzoxazepin-3-il]metil}-4-metil-1,3-tiazol-5-il)propiónico



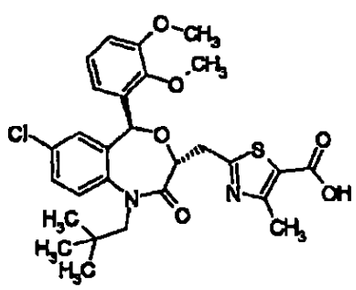
De conformidad con una manera similar a la del ejemplo 1, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 2.28 (3H, s), 2.64 (2H, t, J = 7.6 Hz), 3.02 (2H, t, J = 7.6 Hz), 3.31-3.44 (2H, m), 3.52 (1H, dd, J = 15.0, 6.0 Hz), 3.63 (3H, s), 3.89 (3H, s), 4.24-4.30 (1H, m), 4.51 (1H, d, J = 13.8 Hz), 6.31 (1H, s), 6.57 (1H, d, J = 2.1 Hz), 6.97 (1H, dd, J = 6.6, 3.2 Hz), 7.14-7.22 (2H, m), 7.24-7.33 (2H, m).

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EJEMPLO 126

Acido 2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-4-metil-1,3-tiazol-5-carboxílico

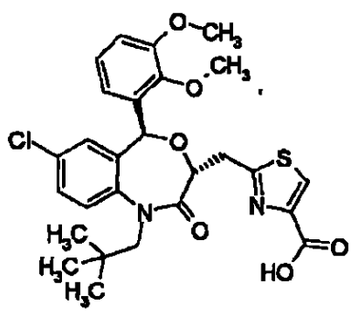


De conformidad con una manera similar a la del ejemplo 16, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 2.68 (3H, s), 3.36 (1H, 5 d, J = 13.9 Hz), 3.47 (1H, dd, J = 15.0, 6.9 Hz), 3.55-3.66 (4H, m), 3.89 (3H, s), 4.32 (1H, t, J = 6.4 Hz), 4.52 (1H, d, J = 13.9 Hz), 6.33 (1H, s), 6.59 (1H, d, J = 2.1 Hz), 6.99 (1H, dd, J = 7.5, 2.3 Hz), 7.13-7.23 (2H, m), 7.28-7.35 (2H, m).

EJEMPLO 127

Acido 2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-4-carboxílico



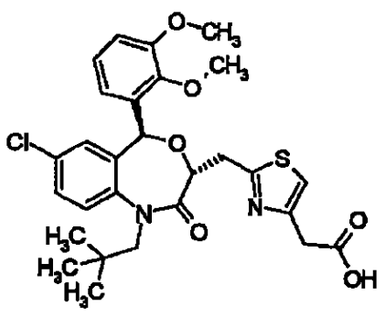
De conformidad con una manera similar a la del ejemplo 22, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 3.35 (1H, d, J = 13.9 Hz), 3.50-3.69 (5H, m), 3.89 (3H, s), 4.34 (1H, t, J = 6.4 Hz), 4.50 (1H, d, J = 13.9 Hz), 6.33 (1H, s), 6.58 (1H, d, J = 2.1 Hz), 6.99 (1H, dd, J = 8.0, 1.4 Hz), 7.07-7.12 (1H, m), 7.18 (1H, t, J = 7.9 Hz), 7.25-7.35 (2H, m), 8.19 (1H, s).

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661

EJEMPLO 128

Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-4-il)acético

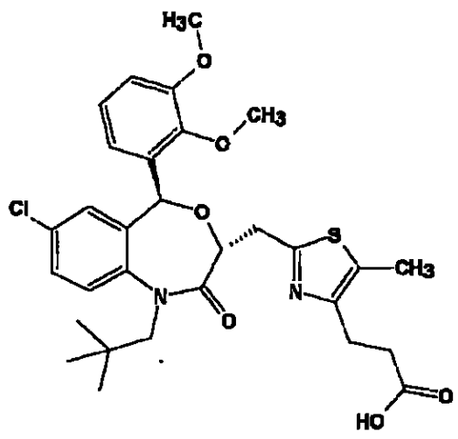


De conformidad con una manera similar a la del ejemplo 16, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 3.38 (1H, d, J = 13.9 Hz), 3.48 (1H, dd, J = 15.3, 6.6 Hz), 3.60-3.72 (4H, m), 3.79 (2H, s), 3.89 (3H, s), 4.34 (1H, t, J = 6.5 Hz), 4.49 (1H, d, J = 13.9 Hz), 6.33 (1H, s), 6.60 (1H, s), 6.99 (1H, dd, J = 6.9, 2.9 Hz), 7.02 (1H, s), 7.13-7.23 (2H. m), 7.33 (2H, s).

EJEMPLO 129

Acido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-5-metil-1,3-tiazol-4-il)propiónico

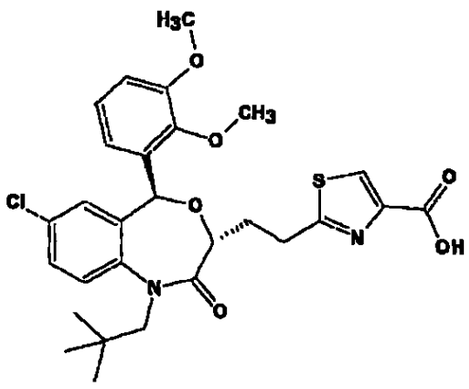


De conformidad con una manera similar a la del ejemplo 20, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 2.32 (3H, s), 2.66-2.73 (2H, m), 2.82-2.90 (2H, m), 3.33-3.44 (2H, m), 3.58 (1H, dd, J = 16.2, 6.6 Hz), 3.63 (3H, s), 3.89 (3H, s), 4.27 (1H, t, J = 6.4 Hz), 4.49 (1H, d, J = 13.9 Hz), 6.31 (1H, s), 6.60 (1H, s), 6.99 (1H, dd, J = 5.8, 3.8 Hz), 7.15-7.23 (2H, m), 7.31-7.39 (2H, m, J = 1.9 Hz).

EJEMPLO 130

Acido 2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3-5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,3-tiazol-4-carboxílico

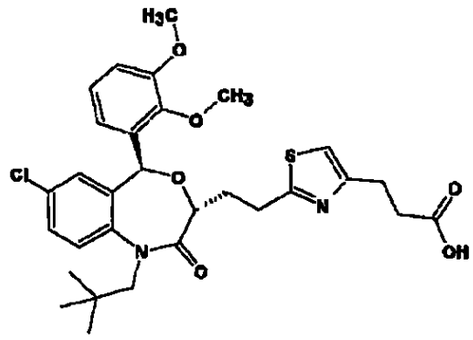


De conformidad con una manera similar a la del ejemplo 22, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 2.22-2.49 (2H, m), 3.08-3.32 (2H, m), 3.35 (1H, d, J = 13.9 Hz), 3.63 (3H, s), 3.90 (3H, s), 3.94 (1H, dd, J = 7.5, 5.3 Hz), 4.50 (1H, d, J = 13.8 Hz), 6.28 (1H, s), 6.61 (1H, d, J = 2.3 Hz), 6.95-7.03 (1H, m), 7.16-7.24 (2H, m), 7.25-7.37 (2H, m), 8.11 (1H, s).

EJEMPLO 131

Acido 3-(2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,3-tiazol-4-il)propiónico

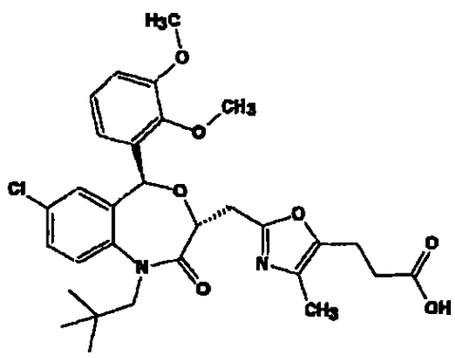


De conformidad con una manera similar a la del ejemplo 88, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 2.18-2.44 (2H, m), 2.64-2.74 (2H, m), 2.94-3.03 (2H, m), 3.04-3.27 (2H, m), 3.36 (1H, d, J= 13.9 Hz), 3.63 (3H, s), 3.89 (3H, s), 3.94 (1H, dd, J = 7.3, 5.7 Hz), 4.52 (1H, d, J = 13.9 Hz), 6.28 (1H, s), 6.60 (1H, d, J = 2.1 Hz), 6.80 (1H, s), 6.99 (1H, dd, J = 7.0, 2.6 Hz), 7.16-7.36 (4H, m).

EJEMPLO 132

Acido 3-{2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-{2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-4-metil-1,3-oxazol-5-il)propiónico



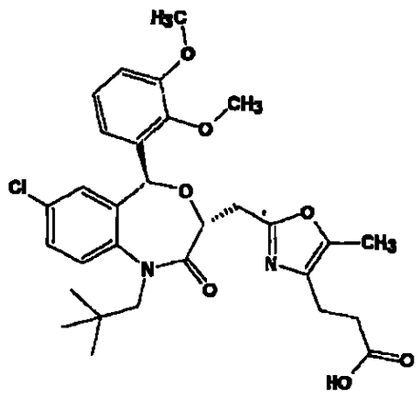
De conformidad con una manera similar a la del ejemplo 29, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (9H, s), 2.05 (3H, s), 2.63 (2H, t), 2.88 (2H, t, J = 7.4 Hz), 3.16-3.32 (2H, m), 3.36 (1H, d, J = 13.8 Hz), 3.62 (3H, s), 3.88 (3H, s), 4.38 (1H, t, J = 6.8 Hz), 4.51 (1H, d, J = 13.9 Hz), 6.30 (1H, s), 6.57 (1H, d, J = 1.5 Hz), 6.96 (1H, dd, J = 8.1, 1.3 Hz), 7.03 (1H, dd, J = 7.8, 1.2 Hz), 7.16 (1H, t, J = 7.9 Hz), 7.27-7.36 (2H, m).

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666

EJEMPLO 133

Acido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-5-metil-1,3-oxazol-4-il)propiónico

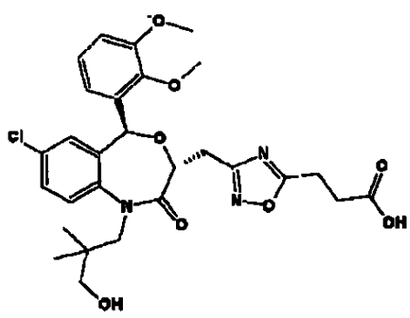


De conformidad con una manera similar a la del ejemplo 38, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (9H, s), 2.22 (3H, s), 2.59-2.72 (4H, m), 3.17 (1H, dd, J = 16.0, 6.4 Hz), 3.31-3.45 (2H, m), 3.63 (3H, s), 3.89 (3H, s), 4.40 (1H, t, J = 6.8 Hz), 4.48 (1H, d, J = 13.9 Hz), 6.30 (1H, s), 6.59 (1H, d, J = 2.1 Hz), 6.97 (1H, dd, J = 7.9, 1.5 Hz), 7.08 (1H, dd, J = 7.7, 1.5 Hz), 7.16 (1H, t, J = 7.9 Hz), 7.32-7.42 (2H, m).

EJEMPLO 134

Acido 3-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)propiónico

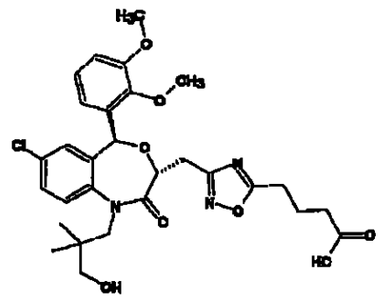


De conformidad con una manera similar a la del ejemplo 60, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 2.89 (2H, t, J = 7.2 Hz), 3.11-3.27 (4H, m), 3.34-3.44 (2H, m), 3.58-3.67 (4H, m), 3.89 (3H, s), 4.39-4.51 (2H, m), 6.19 (1H, s), 6.60 (1H, d, J = 1.7 Hz), 6.98 (1H, dd, J = 8.0, 1.6 Hz), 7.07-7.12 (1H, m), 7.18 (1H, t, J = 7.9 Hz), 7.32-7.41 (2H, m).

EJEMPLO 135

Acido 4-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)butanoico

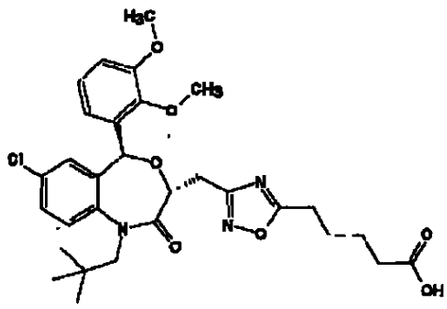


De conformidad con una manera similar a la del ejemplo 60, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.05 (3H, s), 2.08-2.19 (3H, m), 2.49 (2H, t, J = 7.2 Hz), 2.95 (2H, t, J = 7.3 Hz), 3.12-3.28 (2H, m), 3.34-3.44 (2H, m), 3.59-3.67 (4H, m), 3.89 (3H, s), 4.41-4.52 (2H, m), 6.20 (1H, s), 6.60 (1H, d, J = 1.5 Hz), 6.98 (1H, dd, J = 8.0, 1.6 Hz), 7.09 (1H, dd, J = 7.8, 1.4 Hz), 7.17 (1H, t, J = 7.9 Hz), 7.35-7.38 (2H, m).

EJEMPLO 136

Acido 5-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)pentanoico



(1) Clorhidrato de 1-etil-3-(3-dimetilaminopropil) carbodiimida (23.0 g, 0.120 moles) y 1H-1,2,3-benzotriazol-1-olato de amonio (18.26 g, 0.120 moles) se añadieron a una solución de ácido [(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acético (46.19 g, 0.100 moles) en DMF (500 ml) y la mezcla se agitó durante 20 horas. La solución de reacción se concentró bajo presión reducida, se extrajo con acetato de etilo, se lavó con agua y una solución acuosa saturada de cloruro de sodio, y después se secó sobre sulfato de magnesio.Después de concentrarse bajo presión reducida, el residuo se purificó por cromatografía en columna sobre gel de sílice y después se recristalizó a partir de acetato de etilo-hexano para obtener 2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetamida (32.43 g) como un

cristal.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9 H, s), 2.65-2.73 (1H, m), 2.84-2.92 (1H, m), 3.37 (1H, d, J = 13.8 Hz), 3.62 (3H, s), 3.89 (3H, s), 4.39 (1 H, dd, J = 7.3, 5.9 Hz), 4.50 (1H, d, J = 13.9 Hz), 5.27 (1H, s), 5.86 (1 H, s), 6.28 (1H, s), 6.61 (1H, d, J = 2.1 Hz), 6.99 (1H, dd, J = 6.7, 3.1 Hz), 7.18-7.23 (2H, m), 7.31-7.36 (2 H, m).

(2) 1-1'-Carbonilobis-1H-imidazol (9.85 g, 0.0607 moles) y bromuro de alilo (20.7 ml, 0.243 moles) se añadieron a una solución de 2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetamida (14.0 g, 0.0304 moles) obtenido en el ejemplo 136-(1) en acetonitrilo (140 ml), y la mezcla se calentó a reflujo durante 3 horas. Después de reposar hasta enfriarse, la solución de reacción se extrajo con acetato de etilo, se lavó con ácido clorhídrico acuoso 1 N y una solución acuosa saturada de cloruro de sodio, y después se secó sobre sulfato de magnesio. El extracto se filtró con gel de sílice y se concentró bajo presión reducida. El residuo se recristalizó a partir de acetato de etilo-hexano para obtener [(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetonitrilo (12.31 g).

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9 H, s), 2.78-2.88 (1H, m),

2.89-2.99 (1H, m), 3.38 (1H, d, J = 13.9 Hz), 3.63 (3H, s), 3.90 (3H, s), 4.21 (1H, dd, J = 7.6, 5.6 Hz), 4.51 (1H, d, J = 13.9 Hz), 6.30 (1H, s), 6.65 (1H, d, J = 2.1 Hz), 7.01 (1H, d, J = 7.9 Hz), 7.19-7.41 (4H, m).

(3) Se añadió gota a gota trietilamina (23.66 ml, 0.169 moles) a una solución de clorhidrato de hidroxilamina (11.77 g, 0.169 moles) en DMSO (150 ml) bajo enfriamiento con hielo y la mezcla se agitó durante 30 minutos. Los precipitados se filtraron. Al filtrado se añadió [(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetonitrilo (15.0 g, 0.0339 moles) obtenido en el ejemplo 136-(2) y la mezcla se agitó a 80°C durante 4 horas. La solución de reacción se extrajo con acetato de etilo, se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener 2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-N'-hidroxietanimidoamida (17.5 g) como una sustancia amorfa, que se uso en la siguiente reacción sin purificación.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9 H, s), 2.56-2.64 (1H, m), 2.79 (1H, dd, J = 14.4, 7.1 Hz), 3.36 (1H, d, J = 13.9 Hz), 3.60-3.65 (3H, m), 3.89 (3H, s), 4.07-4.14 (1H, m), 4.50 (1H, d, J = 13.9 Hz), 4.98 (2H, s), 6.25-6.29 (1H, m), 6.60 (1H,

d, J = 2.1 Hz), 6.99 (1H, dd, J = 5.9, 3.9 Hz), 7.16-7.23 (2H, m), 7.29-7.35 (2H, m).

(4) Trietilamina (0.83 ml, 5.95 mmoles) y 6-cloro-6-oxohexanoato de metilo (0.69 g, 3.85 mmoles) se añadieron gota a gota a una solución de 2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-N'-hidroxietanimidoamida (1.67 g, 3.5 mmoles) obtenida en el ejemplo 136-(3) en THF (15 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 2.5 horas. La solución de reacción se concentró bajo presión reducida, se añadió agua (15 ml) a la misma, y la mezcla se calentó a reflujo durante 11 horas. La solución de reacción se extrajo con acetato de etilo, se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó sobre sulfato de magnesio. Después de concentrarse bajo presión reducida, el residuo se purificó por cromatografía en columna sobre gel de sílice para obtener 5-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)pentanoato de metilo (1.04 g).

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9 H, s), 1.63-1.91 (4H, m), 2.36 (2H, t, J = 7.2 Hz), 2.87 (2H, t, J = 7.4 Hz), 3.20-3.42 (3H, m), 3.62 (3H, s), 3.67 (3H, s), 3.88 (3H, s), 4.43 (1H,

t, J = 6.8 Hz), 4.51 (1H, d, J = 13.9 Hz), 6.31 (1H, s), 6.58 (1H, s), 6.97 (1H, dd, J = 8.0, 1.6 Hz), 7.07 (1H, dd, J = 7.7, 1.5 Hz), 7.15 (1H, t, J = 7.9 Hz), 7.29-7.37 (2H, m).

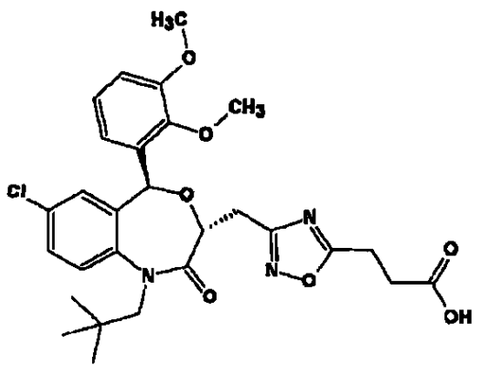
(5) Una solución acuosa 2 N de hidróxido de sodio (2.60 ml, 5.20 mmoles) se añadió a una solución de 5-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)pentanoato de metilo (1.04 g, 1.73 mmoles) obtenida en el ejemplo 136-(4) en etanol (10 ml) y la mezcla se agitó durante 13 horas. La solución de reacción se diluyó con agua y después se lavó con éter dietílico. La solución extraída se acidificó con ácido clorhídrico acuoso 6 N, se extrajo con acetato de etilo, se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener ácido 5-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)pentanoico (0.89 g).

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 1.66-1.93 (4H, m), 2.39 (2H, t, J = 7.3 Hz), 2.88 (2H, t, J = 7.4 Hz), 3.19-3.41 (3H, m), 3.62 (3H, s), 3.88 (3H, s), 4.43 (1H, t, J = 6.8 Hz), 4.51 (1H, d, J = 13.9 Hz), 6.31 (1H, s), 6.58 (1H, d, J

= 1.5 Hz), 6.96 (1H, dd, J = 7.9, 1.7 Hz), 7.07 (1H, dd, J = 7.8, 1.6 Hz), 7.14 (1H, t, J = 7.8 Hz), 7.28-7.37 (2H, m).

EJEMPLO 137

Acido 3-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)propiónico



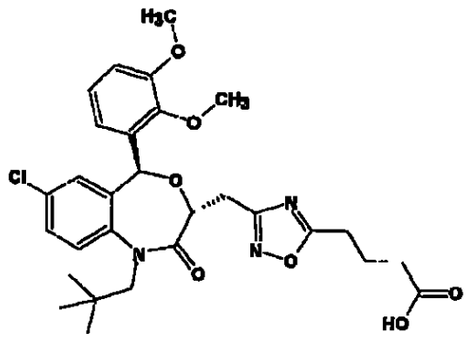
De conformidad con una manera similar a la del ejemplo 136, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 2.90 (2H, t, J = 7.3 Hz), 3.16 (2H, t, J = 7.3 Hz), 3.21-3.40 (3H, m), 3.62 (3H, s), 3.88 (3H, s), 4.42 (1H, t, J= 6.7 Hz), 4.51 (1H, d, J = 13.9 Hz), 6.31 (1H, s), 6.59 (1H, d, J = 1.5 Hz), 6.97 (1H, dd, J = 8.0, 1.6 Hz), 7.06-7.11 (1H, m), 7.16 (1H, t, J = 7.9 Hz), 7.29-7.37 (2H, m).

668
675

EJEMPLO 138

Acido 4-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)butanoico



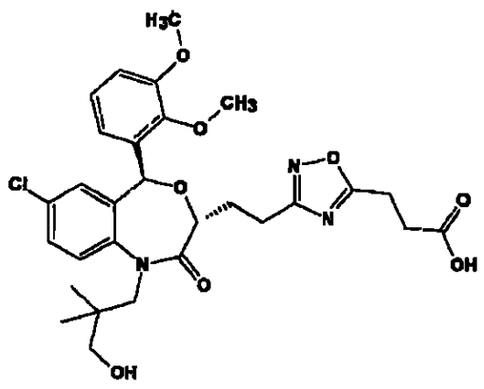
De conformidad con una manera similar a la del ejemplo 136, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 2.08-2.20 (2H, m), 2.49 (2H, t, J = 7.1 Hz), 2.95 (2H, t, J = 7.3 Hz), 3.19-3.42 (3H, m), 3.62 (3H, s), 3.88 (3H, s), 4.44 (1H, t, J = 6.8 Hz), 4.51 (1H, d, J = 13.9 Hz), 6.31 (1H, s), 6.59 (1H, s), 6.97 (1H, dd, J = 8.0, 1.8 Hz), 7.08 (1H, dd, J = 7.8, 1.4 Hz), 7.16 (1H, t, J = 7.9 Hz), 7.30-7.36 (2H, m).

667
676

EJEMPLO 139

Acido 3-(3-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil)-1,2,4-oxadiazol-5-il)propiónico

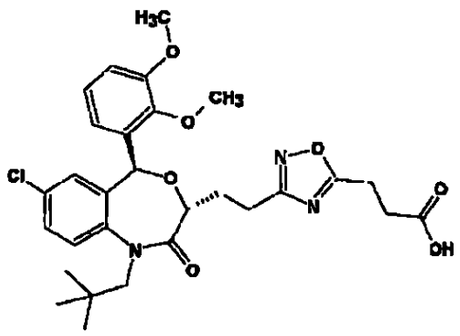


De conformidad con una manera similar a la del ejemplo 60, 1 se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.15-2.41 (2H, m), 2.77-2.98 (4H, m), 3.07-3.20 (3H, m), 3.37 (1H, d, J = 14.3 Hz), 3.59-3.66 (4H, m), 3.89 (3H, s), 3.95 (1H, dd, J = 7.7, 5.3 Hz), 4.46 (1H, d, J = 14.3 Hz), 6.15 (1H, s), 6.60 (1H, d, J = 2.3 Hz), 6.95-7.02 (1H, m), 7.17-7.22 (2H, m, J = 4.1, 4.1 Hz), 7.29-7.39 (2H, m).

EJEMPLO 140

Acido 3-(3-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,2,4-oxadiazol-5-il)propiónico



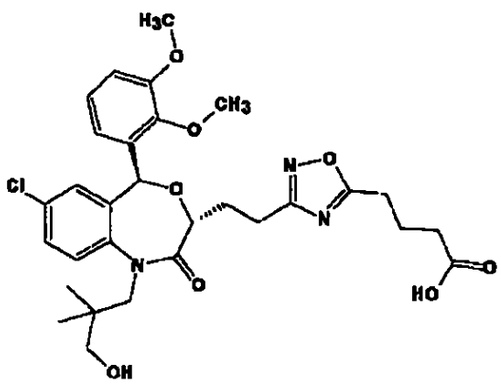
De conformidad con una manera similar a la del ejemplo 136, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (9H, s), 2.14-2.41 (2H, m), 2.77-2.98 (4H, m), 3.11 (2H, t, J = 7.3 Hz), 3.34 (1H, d, J = 13.9 Hz), 3.63 (3H, s), 3.89 (3H, s), 3.93 (1H, dd, J= 7.9, 5.1 Hz), 4.51 (1H, d, J = 13.8 Hz), 6.27 (1H, s), 6.60 (1H, d, J = 2.1 Hz), 6.98 (1H, dd, J = 7.0, 2.6 Hz), 7.15-7.24 (2H, m), 7.28-7.36 (2H, m).

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EJEMPLO 141

Acido 4-(3-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,2,4-oxadiazol-5-il)butanoico

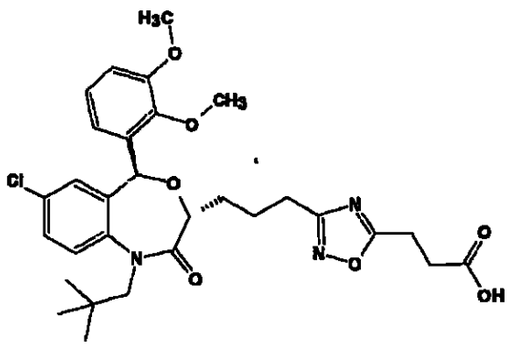


De conformidad con una manera similar a la del ejemplo 60, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 2.02-2.14 (3H, m), 2.18-2.42 (2H, m), 2.45 (2H, t, J = 7.2 Hz), 2.77-2.99 (4H, m), 3.15 (1H, d, J = 12.1 Hz), 3.37 (1H, d, J = 14.3 Hz), 3.58-3.66 (4H, m), 3.89 (3H, s), 3.95 (1H, dd, J = 7.8, 5.4 Hz), 4.46 (1H, d, J = 14.3 Hz), 6.15 (1H, s), 6.60 (1H, d, J = 2.3 Hz), 6.95-7.03 (1H, m), 7.16-7.23 (2H, m),7.29-7.39 (2H,m).

EJEMPLO 142

Acido 3-(3-{3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]propil}-1,2,4-oxadiazol-5-il)propiónico

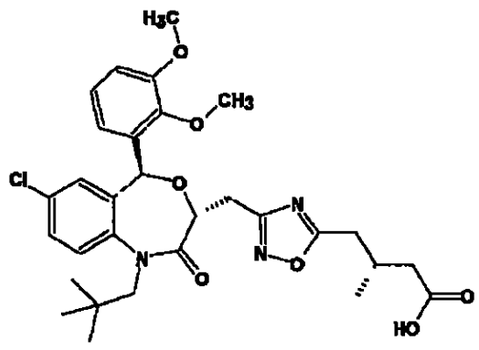


De conformidad con una manera similar a la del ejemplo 136, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (9H, s), 1.70-2.03 (4H, m), 2.66-2.78 (2H, m), 2.90 (2H, t, J = 7.2 Hz), 3.15 (2H, t, J = 7.2 Hz), 3.34 (1H, d, J = 13.9 Hz), 3.62 (3H, s), 3.85 (1H, dd, J = 7.5, 4.8 Hz), 3.89 (3H, s), 4.50 (1H, d, J = 13.9 Hz), 6.24 (1H, s), 6.59 (1H, d, J = 2.3 Hz), 6.98 (1H, dd, J= 7.7, 2.1 Hz), 7.15-7.36 (4H, m).

EJEMPLO 143

Acido (3R)-4-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)-3-metilbutanoico

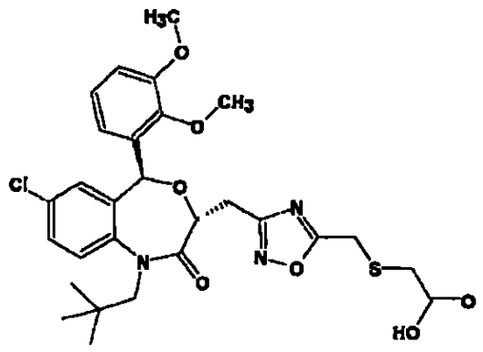


De conformidad con una manera similar a la del ejemplo 136, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 1.07 (3H, d, J = 6.6 Hz), 2.33 (1H, dd, J = 15.6, 7.2 Hz), 2.41-2.63 (2H, m), 2.84 (1H, dd, J = 15.3, 6.9 Hz), 2.96 (1H, dd, J = 15.3, 6.6 Hz), 3.21-3.42 (3H, m), 3.62 (3H, s), 3.88 (3H, s), 4.45 (1H, t, J = 6.8 Hz), 4.51 (1H, d, J = 13.9 Hz), 6.31 (1H, s), 6.58 (1H, s), 6.96 (1H, dd, J= 7.9, 1.7 Hz), 7.06 (1H, dd, J = 7.9, 1.5 Hz), 7.14 (1H, t, J = 7.9 Hz), 7.29-7.37 (2H, m).

EJEMPLO 144

Acido {[(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3-5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)metil]tio}acético



(1) Tioacetato de potasio (0.76 g, 5.97 mmoles) se añadió a una solución de (3R,5S)-7-cloro-3-{[5-(clorometil)-1,2,4-oxadiazol-3-il]metil}-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-1,5-dihidro-4,1-benzoxazepin-2(3H)-ona (3.8 g, 4.98 mmoles) sintetizada como en el ejemplo 136 en DMF (30 ml), y la mezcla se agitó a temperatura ambiente durante 12 horas. La solución de reacción se extrajo con acetato de etilo, se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (4:1)] para obtener acetato de S-[(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-

tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)metilo] (2.45 g, 4.26 mmoles, 86%) como un polvo no cristalino blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 2.40 (3H, s), 3.30 (2H, dd, J = 6.7, 2.4 Hz), 3.37 (1H, d, J = 13.9 Hz), 3.62 (3H, s), 3.88 (3H, s), 4.28 (2H, s), 4.42 (1H, t, J = 6.8 Hz), 4.51 (1H, d, J = 13.8 Hz), 6.30 (1H, s), 6.58 (1H, d, J = 1.9 Hz), 6.97 (1H, dd, J= 8.1, 1.5 Hz), 7.05 (1H, dd, J = 7.8, 1.0 Hz), 7.17 (1H, t, J = 8.0 Hz), 7.28-7.37 (2H, m).

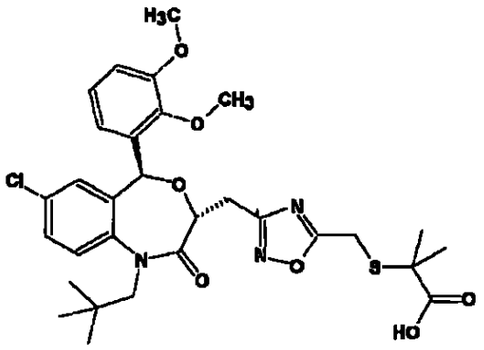
(2) Una solución acuosa 2 N de hidróxido de sodio (1.74 ml, 3.48 mmoles) se añadió a una solución de acetato de S-[(3-{[(3R,58)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)metilo] (1.0 g, 1.74 mmoles) en metanol (10 ml), y la mezcla se agitó durante 1.5 horas. La solución de reacción se extrajo con acetato de etilo, se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. Bromoacetato de etilo (0.12 ml, 1.04 mmoles) y carbonato de potasio (0.24 g, 1.74 mmoles) se añadieron a una solución del residuo en THF (10 ml), y la mezcla se agitó durante 17 horas. La solución de reacción se extrajo con acetato de etilo, se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de

magnesio, y después se concentró bajo presión reducida. El residuo se disolvió en etanol (10 ml), se añadió una solución acuosa 2 N de hidróxido de sodio (1.16 ml, 2.33 mmoles), y la mezcla se agitó durante 5 horas. La solución de reacción se diluyó con agua y después se lavó con éter dietílico. El extracto se acidificó con ácido clorhídrico acuoso 1 N, se extrajo con acetato de etilo, se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener ácido {[(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)metil]tio}acético (413 mg, 80%).

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 3.26 (1H, dd, J = 15.7, 6.7 Hz), 3.34-3.44 (4H, m), 3.63 (3H, s), 3.89 (3H, s), 4.00 (2H, s), 4.44-4.54 (2H, m), 6.31 (1H, s), 6.59 (1H, s), 6.97 (1H, dd, J = 8.0, 1.6 Hz), 7.07 (1H, dd, J = 7.9, 1.5 Hz), 7.16 (1H, t, J = 8.0 Hz), 7.34 (2H, d, J = 1.3 Hz).

EJEMPLO 145

Acido 2-{[(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}1,2,4-oxadiazol-5-il)metil]tio}-2-metilpropiónico



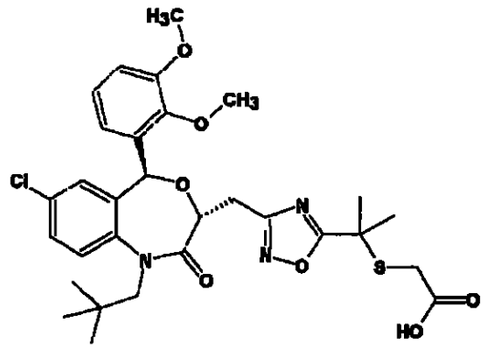
De conformidad con una manera similar a la del ejemplo 144, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (9H, s), 1.54 (3H, s), 1.56 (3H, s), 3.20 (1H, dd, J = 15.4, 6.2 Hz), 3.33-3.47 (2H, m), 3.63 (3H, s), 3.89 (3H, s), 4.01 (2H, s), 4.44-4.53 (2H, m), 6.30 (1H, s), 6.60, (1H, s), 6.98 (1H, dd, J= 7.8, 1.8 Hz), 7.12 (1H, dd, J = 7.7, 1.7 Hz), 7.18 (1H, t, J = 1.8 Hz), 7.34 (2H, d, J = 0.9 Hz).

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685

EJEMPLO 146

Acido {[1-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)-1-metiletil]tio}acético

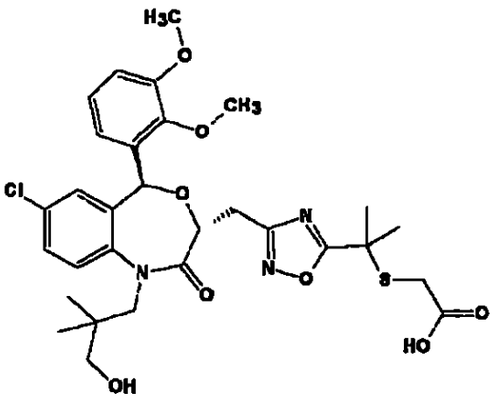


De conformidad con una manera similar a la del ejemplo 144, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (9H, s), 1.78 (3H, s), 1.81 (3H, s), 3.15 (1H, dd, J = 15.8, 5.3 Hz), 3.28-3.53 (4H, m), 3.64 (3H, s), 3.89 (3H, s), 4.47 (1H, d, J = 13.9 Hz), 4.53 (1H, dd, J = 8.7, 5.3 Hz), 6.30 (1H, s), 6.62 (1H, s), 6.98 (1H, dd, J = 7.0, 2.8 Hz), 7.13-7.22 (2H, m), 7.36 (2H, d, J = 1.3 Hz).

EJEMPLO 147

Acido {[1-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)-1-metiletil]tio}acético

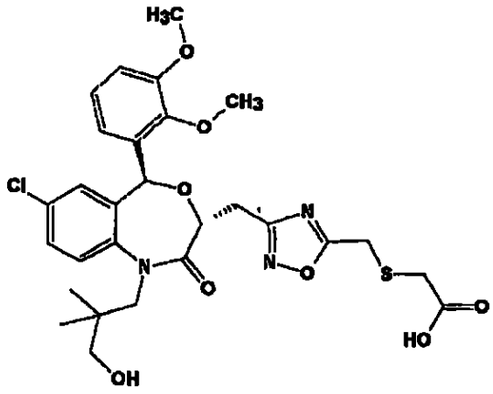


De conformidad con una manera similar a la del ejemplo 144, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.67 (3H, s), 1.04 (3H, s), 1.78 (3H, s), 1.79 (3H, s), 3.16-3.27 (2H, m), 3.35-3.49 (4H, m), 3.59-3.67 (4H, m), 3.89 (3H, s), 4.41-4.53 (2H, m), 6.19 (1H, s), 6.61 (1H, s), 6.99 (1H, dd, J= 7.9, 1.9 Hz), 7.11 (1H, dd, J = 7.8, 1.8 Hz), 7.18 (1H, t, J = 7.9 Hz), 7.34-7.43 (2H, m).

EJEMPLO 148

Acido {[(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il)metil}-1,2,4-oxadiazol-5-il)metil]tio}acético

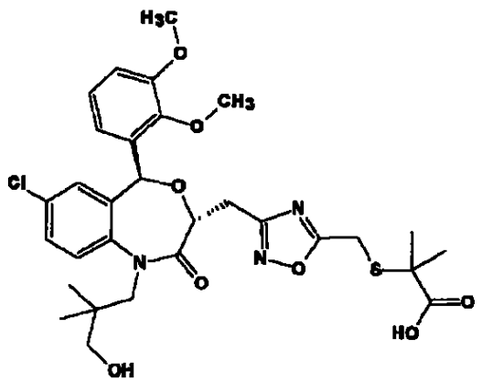


De conformidad con una manera similar a la del ejemplo 144, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.66 (3H, s), 1.05 (3H, s), 3.17-3.32 (2H, m), 3.34-3.48 (4H, m), 3.58-3.68 (4H, m), 3.89 (3H, s), 4.00 (2H, s), 4.42-4.53 (2H, m), 6.19 (1H, s), 6.61 (1H, d, J = 1.3 Hz), 6.98 (1H, dd, J = 8.1, 1.5 Hz), 7.07 (1H, dd, J = 7.7, 1.5 Hz), 7.17 (1H, t, J = 8.0 Hz), 7.33-7.42 (2H, m).

EJEMPLO 149

Acido 2-{[(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)metil]tio}-2-metilpropiónico

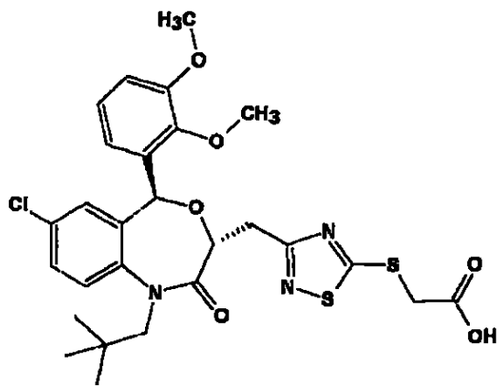


De conformidad con una manera similar a la del ejemplo 144, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.66 (3H, s), 1.04 (3H, s), 1.54 (3H, s), 1.54 (3H, s), 3.14-3.29 (2H, m), 3.34-3.47 (2H, m), 3.57-3.66 (4H, m), 3.89 (3H, s), 4.03 (2H, s), 4.42-4.52 (2H, m), 6.19 (1H, s), 6.60 (1H, d, J= 1.1 Hz), 6.98 (1H, dd, J = 8.1, 1.7 Hz), 7.09 (1H, dd, J = 7.7, 1.5 Hz), 7.17 (1H, t, J = 7.9 Hz), 7.33-7.41 (2H, m).

EJEMPLO 150

Acido [(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-triadiazol-5-il)tio]acético



(1) Se añadió yoduro de metilo (0.65 ml, 10.48 mmoles) a una solución de 2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etanotioamida (1.0 g, 2.10 mmoles) obtenida como en el ejemplo 16-(2) en acetona (10 ml), y la mezcla se agitó durante 14 horas. Después de que la solución de reacción se concentró bajo presión reducida, se añadieron acetato de amonio (0.81 g, 10.48 mmoles) y metanol (10 ml) a la misma y la mezcla se calentó a reflujo durante 4 horas. Después, percloro metilmercaptano (0.23 ml, 2.1 mmoles) se añadió a una solución del residuo en diclorometano, una solución de hidróxido de sodio (0.375 g, 9.38 mmoles) en agua (3 ml) se añadió lentamente gota a gota a la misma a -10°C. La solución de reacción se agitó a -10°C durante 2 horas y

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690

después a temperatura ambiente durante 30 minutos. La solución de reacción se extrajo con acetato de etilo, se lavó sucesivamente con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (95:5-85:15)] para obtener (3R,5S)-7-cloro-3-[(5-cloro-1,2,4-tiadiazol-3-il)metil]-5-(2,3-dimetoxifenil)-1-(2,2,dimetilpropil)-1,5-dihidro-4,1-benzoxazepin-2(3H)-ona (0.46 g, 0.857 mmoles, 41%) como un sólido no cristalino blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 3.33-3.48 (2H, m), 3.55-3.66 (4H, m), 3.89 (2H, s), 4.50 (1H, d, J = 13.8 Hz), 4.58 (1H, t, J = 6.7 Hz), 6.31 (1H, s), 6.59 (1H, d, J = 1.1 Hz), 6.93-7.04 (2H, m), 7.15 (1H, t, J = 8.0 Hz), 7.30-7.38 (2H, m).

(2) Tioglicolato de etilo (113 ml, 1.03 mmoles) y carbonato de potasio (178 mg, 1.29 mmoles) se añadieron a una solución de (3R,5S)-7-cloro-3-[(5-cloro-1,2,4-tiadiazol-3-il)metil]-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-1,5-dihidro-4,1-benzoxazepin-2(3H)-ona (0.46 g, 0.857 mmoles) obtenido en el ejemplo 150-(1) en THF (10 ml), y la mezcla se agitó a 45°C durante 16 horas. La solución de reacción se extrajo con acetato de etilo, se lavó sucesivamente con agua

y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (95:5-85:15)] para obtener [(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-tiadiazol-5-il)tio]acetato de etilo (0.48 g, 0.774 mmoles, 90%) como un sólido no cristalino blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 1.26 (3H, t, J = 7.2 Hz), 3.32-3.43 (2H, m), 3.57 (1H, dd, J = 15.6, 6.9 Hz), 3.63 (3H, s), 3.89 (3H, s), 4.01 (2H, s), 4.18 (2H, q, J = 7.2 Hz), 4.50 (1H, d, J = 13.9 Hz), 4.58 (1H, t, J = 6.7 Hz), 6.31 (1H, s), 6.59 (IH, s), 6.96 (1H, dd, J = 8.1, 1.5 Hz), 7.04 (1H, dd, J = 7.8, 1.4 Hz), 7.15 (1H, t, J = 8.0 Hz), 7.34 (2H, d, J = 1.3 Hz).

(3) Una solución acuosa 2 N de hidróxido de sodio (1.16 ml, 2.32 mmoles) se añadió a una solución de [(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-tiadiazol-5-il)tio]acetato de etilo (0.48 g, 0.774 mmoles) obtenido en el ejemplo 150-(2) en una mezcla de etanol (5 ml) y THF (5 ml), y la mezcla se agitó durante 1 hora. La solución de reacción se extrajo con agua y después

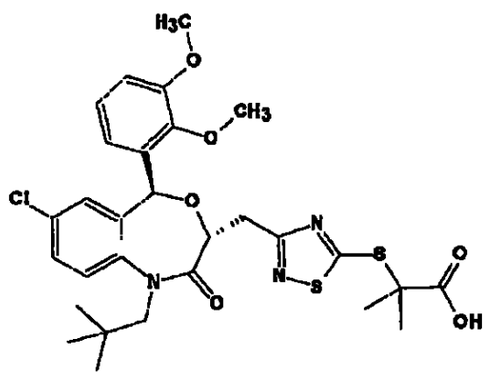
se lavó con éter dietílico. La capa acuosa se acidificó con ácido clorhídrico acuoso 1 N, se extrajo con acetato de etilo, se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se recristalizó a partir de etanol-hexano para obtener ácido [(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-tiadiazol-5-il)tio]acético (374 mg, 0.632 mmoles, 82%) como un cristal incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 3.34-3.45 (2H, m), 3.57-3.68 (4H, m), 3.89 (3H, s), 3.93 (2H, s), 4.49 (1H, d, J = 13.9 Hz), 4.56 (1H, dd, J = 7.2, 6.2 Hz), 6.31 (1H, s), 6.61 (1H, s), 6.97 (1H, dd, J = 8.1, 1.5 Hz), 7.04 (1H, dd, J = 7.7, 1.3 Hz), 7.16 (1H, t, J = 7.9 Hz), 7.33-7.38 (2H, m).

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EJEMPLO 151

Acido 2-[(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-tiadiazol-5-il)tio]-2-metilpropiónico



(1) 3-mercaptopropionato de etilo (0.28 ml, 2.2 mmoles) y carbonato de potasio (0.21 g, 1.5 mmoles) se añadieron a una solución de (3R,5S)-7-cloro-3-[(5-cloro-1,2,4-tiadiazol-3-il)metil]-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-1,5-dihidro-4,1-benzoxazepin-2(3H)-ona (0.54 g, 1.0 mmoles) obtenido en el ejemplo 150-(1) en THF (10 5 ml), y la mezcla se agitó a 45°C durante 13.5 horas. La solución de reacción se extrajo con acetato de etilo, se lavó sucesivamente con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se disolvió en etanol, se añadió una solución acuosa de hidróxido de sodio 2 N (0.836 ml, 1.67 mmoles), y la mezcla se agitó durante 1 hora. La solución de reacción se extrajo

con acetato de etilo, se lavó sucesivamente con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. Al residuo se añadió 2-bromo-2-metilpropionato de etilo (0.18 ml, 1.25 mmoles), carbonato de potasio (0.17 g, 1.25 mmoles) y THF (10 ml), y la mezcla se calentó a reflujo durante 14 horas. La solución de reacción se extrajo con acetato de etilo, se lavó sucesivamente con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice [solvente de revelado: hexano-acetato de etilo (85:15-80:20)] para obtener 2-[(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-tiadiazol-5-il)tio]-2-metilpropionato de etilo (0.47 g, 87%).

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 1.16 (3H, t, J = 7.1 Hz), 1.66 (3H, s), 1.68 (3H, s), 3.35-3.44 (2H, m), 3.55 (1H, dd, J = 15.6, 6.6 Hz), 3.62 (3H, s), 3.88 (3H, s), 4.06 (2H, ddd, J = 14.2, 7.1, 1.9 Hz), 4.51 (1H, d, J = 13.9 Hz), 4.59 (1H, t, J = 6.8 Hz), 6.30 (1H, s), 6.56 (1H, d, J = 1.9 Hz), 6.93-7.00 (1H, m), 7.13 (1H, t, J = 8.0 Hz), 7.31-7.39 (1H, m).

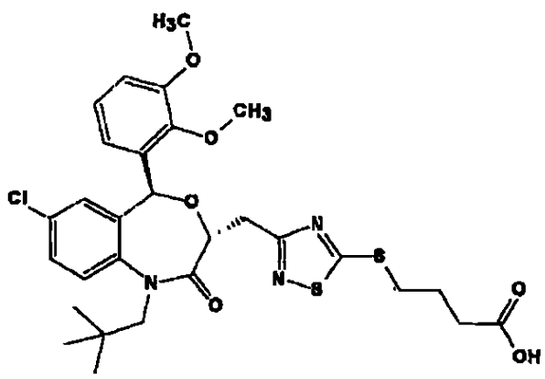
(2) Una solución acuosa de hidróxido de sodio 2 N

(1.1 ml, 2.17 mmoles) se añadió a una solución de 2-[(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-tiadiazol-5-il)tio]-2-metilpropionato de etilo (0.47 g, 0.725 mmoles) obtenida en el ejemplo 151-(1) en etanol (10 ml), y la mezcla se agitó durante 2 horas. La solución de reacción se extrajo con agua y después se lavó con éter dietílico. La capa acuosa se acidificó con ácido clorhídrico acuoso 1 N, se extrajo con acetato de etilo, se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida para obtener ácido 2-[(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-tiadiazol-5-il)tio]2-metilpropiónico (332 mg, 74%).

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 1.66 (3H, s), 1.68 (3H, s), 3.34-3.49 (2H, m), 3.56-3.67 (4H, m), 3.89 (3H, s), 4.49 (1H, d, J = 13.9 Hz), 4.57 (1H, t, J = 6.7 Hz), 6.31 (1H, s), 6.58 (1H, d, J=2.1Hz), 6.97 (2H, dd, J=7.1, 5.9 Hz), 7.14 (1H, t, J = 7.9 Hz), 7.31-7.43 (2H, m).

EJEMPLO 152

Acido 4-[(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-tiadiazol-5-il)tio]butanoico

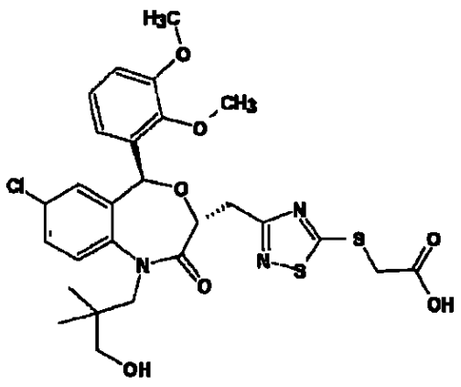


De conformidad con una manera similar a la del ejemplo 151, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (9H, s), 2.03-2.15 (2H, m), 2.50 (2H, t, J = 7.1 Hz), 3.29 (2H, dt, J = 7.0, 2.3 Hz), 3.33-3.43 (2H, m), 3.58 (1H, dd, J = 15.6, 6.9 Hz), 3.63 (3H, s), 3.88 (3H, s), 4.50 (1H, d, J = 13.8 Hz), 4.61 (1H, t, J= 6.7 Hz), 6.31 (1H, s), 6.58 (1H, s),6.96 (1H, dd, J = 8.1, 1.5 Hz), 7.03 (1H, dd, J = 7.9, 1.1 Hz), 7.14 (1H, t, J = 7.9 Hz), 7.33 (2H, d, J = 1.3 Hz).

EJEMPLO 153

Acido [(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-tiadiazol-5-il)tio]acético

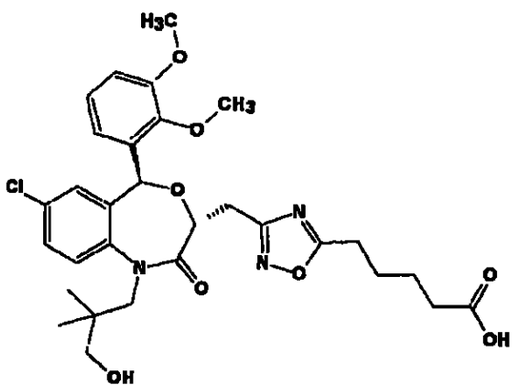


De conformidad con una manera similar a la del ejemplo 150, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 3.20 (1H, d, J = 11.9 Hz), 3.35 (1H, dd, J = 15.9, 5.4 Hz), 3.42 (1H, d, J = 14.3 Hz), 3.59-3.71 (5H, m), 3.89 (3H, s), 3.99 (2H, s), 4.46 (1H, d, J = 14.3 Hz), 4.58 (1H, dd, J = 7.9, 5.5 Hz), 6.19 (1H, s), 6.62 (1H, s), 6.98 (1H, dd, J = 8.0, 1.6 Hz), 7.09 (1H, dd, J = 7.9, 1.5 Hz), 7.17 (1H, t, J = 7.9 Hz), 7.35-7.44 (2H, m).

EJEMPLO 154

Acido 5-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)pentanoico



(1) Trietilamina (1.2 ml, 8.5 mmoles) y 6-cloro-6-oxohexanoato de metilo (0.98 g, 5.5 mmoles) se añadieron gota a gota a una solución de acetato de 3-[(3R,5S)-3-[(2Z)-2-amino-2-(hidroxiimino)etil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (2.67 g, 5.0 mmoles) obtenido en el ejemplo 58-(1) en THF (25 ml) bajo enfriamiento con hielo, y la mezcla se agitó bajo enfriamiento con hielo durante 40 minutos y después a temperatura ambiente durante 1.5 horas. La solución de reacción se concentró bajo presión reducida, se añadió agua (25 ml) y la mezcla se calentó a reflujo durante 18 horas. La solución de reacción se extrajo con acetato de etilo, se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó sobre sulfato de magnesio. Después de concentrarse

bajo presión reducida, el residuo se purificó por cromatografía en columna sobre gel de sílice para obtener 5-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxodiazol-5-il)pentanoato de metilo (1.73 g).

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.03 (3H, s), 1.65-1.90 (4H, m), 2.03 (3H, s), 2.35 (2H, t, J = 7.2 Hz), 2.86 (2H, t, J = 7.3 Hz), 3.29 (2H, ddd, J = 30.5, 15.6, 6.7 Hz), 3.55 (1H, d, J = 13.9 Hz), 3.61 (3H, s), 3.67 (3H, s), 3.74 (1H, d, J = 11.1 Hz), 3.85 (1H, d, J = 11.1 Hz), 3.88 (3H, s), 4.42 (1H, t, J = 6.7 Hz), 4.58 (1H, d, J = 14.1 Hz), 6.30 (1H, s), 6.61 (1H, d, J = 1.5 Hz), 6.97 (1H, dd, J = 7.9, 1.7 Hz), 7.07 (1H, dd, J = 7.8, 1.6 Hz), 7.14 (1H, t, J = 7.9 Hz), 7.29-7.38 (2H, m).

(2) Una solución acuosa 2 N de hidróxido de sodio (5.25 ml, 10.5 mmoles) se añadió a una solución de 5-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxodiazol-5-il)pentanoato de metilo (1.73 g, 2.63 mmoles) obtenida en el ejemplo 154-(1) en etanol (17 ml), y la mezcla se agitó durante 2 horas. La solución de reacción se diluyó con agua y después se lavó con éter dietílico. El extracto se acidificó con ácido clorhídrico acuoso 6 N, se extrajo con acetato de etilo, se lavó con una

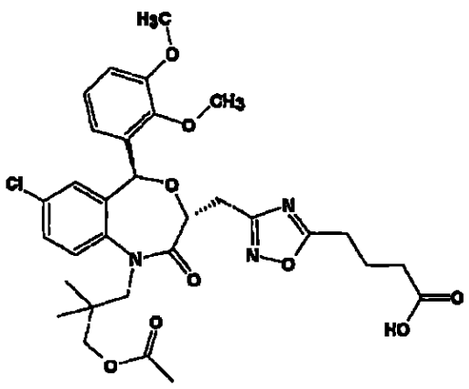
solución de cloruro de sodio acuosa saturada, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice y después se recristalizó a partir de acetato de etilo-hexano para obtener ácido 5-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}1,2,4-oxadiazol-5-il)pentanoico (1.06 g).

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 1.66-1.93 (4H, m), 2.39 (2H, t, J = 7.2 Hz), 2.88 (2H, t, J = 7.4 Hz), 3.12-3.28 (2H, m), 3.33-3.44 (2H, m), 3.57-3.67 (4H, m), 3.89 (3H, s), 4.40-4.53 (2H, m), 6.19 (1H, s), 6.60 (1H, d, J = 1.7Hz), 6.98 (1H, dd, J = 8.1, 1.7 Hz), 7.09 (1H, dd, J = 7.7, 1.5 Hz), 7.16 (1H, t, J = 7.9 Hz), 7.32-7.41 (2H, m).

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EJEMPLO 155

Acido 4-(3-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)butanoico



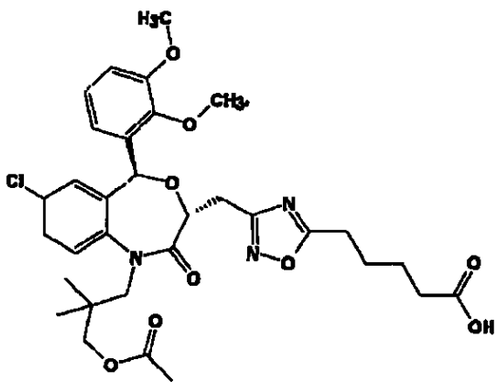
De conformidad con una manera similar a la del ejemplo 14, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.03 (3H, s), 2.03 (3H, s), 2.07-2.19 (2H, m), 2.48 (2H, t, J = 7.2 Hz), 2.95 (2H, t, J = 7.3 Hz), 3.24 (1H, dd, J = 15.6, 7.2 Hz), 3.36 (1H, dd, J = 15.6, 6.6 Hz), 3.55 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.74 (1H, d, J = 11.1 Hz), 3.85 (1H, d, J = 11.3 Hz), 3.88 (3H, s), 4.43 (1H, t, J = 6.7 Hz), 4.57 (1H, d, J = 14.1 Hz), 6.30 (1H, s), 6.62 (1H, s), 6.97 (1H, dd, J = 8.0, 1.6 Hz), 7.05-7.10 (1H, m), 7.15 (1H, t, J = 7.8 Hz), 7.30-7.38 (2H, m).

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EJEMPLO 156

Acido 5-(3-{[(3R,5S)-1-[3-acetoxi-2,2-dimetilpropil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxodiazol-5-il)pentanoico



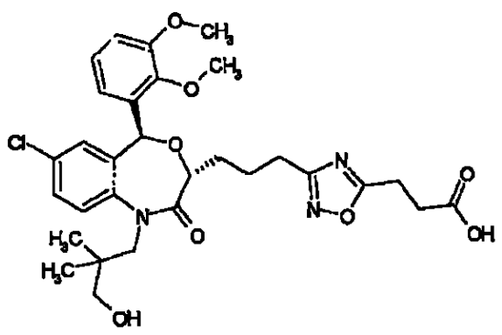
De conformidad con una manera similar a la del ejemplo 14, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.03 (3H, s), 1.67-1.77 (2H, m), 1.81-1.91 (2H, m), 2.03 (3H, s), 2.39 (2H, t, J = 7.2 Hz), 2.88 (2H, t, J = 7.4 Hz), 3.20-3.28 (1H, m), 3.30-3.38 (1H, m), 3.55 (1H, d, J = 14.1 Hz), 3.61 (3H, s), 3.72-3.77 (1H, m), 3.85 (1H, d, J = 11.1 Hz), 3.88 (3H, s), 4.42 (1H, t, J = 6.7 Hz), 4.57 (1H, d, J = 13.9 Hz), 6.30 (1H, s), 6.61 (1H, d, J = 1.7 Hz), 6.97 (1H, dd, J = 7.9, 1.7 Hz), 7.05-7.09 (1H, m), 7.14 (1H, t, J = 7.9 Hz), 7.30-7.37 (2H, m).

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EJEMPLO 157

Acido 3-(3-{3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]propil}-1,2,4-oxadiazol-5-il)propiónico



(1) Se añadió gota a gota (dietoxifosforil)-acetonitrilo (5.03 g, 28.4 mmoles) a una suspensión de hidruro de sodio (1.14 g, 28.4 mmoles) en THF (110 ml) a 0°C. Después de agitarse durante 30 minutos, se añadió acetato de 3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-3-(2-oxoetil)-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (11.01 g, 21.8 mmoles) obtenido en el ejemplo 115-(1) a la misma. Después de agitarse durante 1 hora, la mezcla se diluyó con acetato de etilo, se lavó con una solución acuosa saturada de cloruro de amonio y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener (2E)-4-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-

benzoxazepin-3-il]-2-butenonitrilo (8.15 g, 71%).

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.02 (3H, s), 2.03 (3H, s), 2.64-3.10 (2H, m), 3.49-3.76 (5 H, m), 3.81-4.00 (5 H, m), 4.56 (1H, dd, J = 14.1, 5.1 Hz), 5.37-5.48 (1H, m), 6.26 (1H, d, J = 2.6 Hz), 6.62-6.80 (2H, m), 6.96-7.04 (1H, m), 7.12-7.39 (4H, m).

(2) (2E)-4-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-2-butenonitrilo (8.15 g, 12.4 mmoles) obtenido en el ejemplo 157-(1) se disolvió en metanol (80 ml), se añadió magnesio (1.13 g, 46.4 mmoles) y la mezcla se agitó durante 19 horas. La solución de reacción se diluyó con acetato de etilo, se lavó con ácido clorhídrico acuoso 1 N y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio anhidro y después se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo (40 ml), se añadieron trietilamina (5.1 ml, 36 mmoles) y cloruro de acetilo (2.0 ml, 29.1 mmoles) y la mezcla se agitó durante 5 horas. La solución de reacción se diluyó con acetato de etilo, y la capa orgánica se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener 4-[(3R,5S}-1-(3-

696
705

acetoxi-2,2-dimetilpropil}-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]butanonitrilo (3.89 g, 91%).

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.02 (3H, s), 1.67-2.06 (7H, m), 2.37 (2H, t, J = 6.7 Hz) , 3.52 (1H, d, J = 14.1 Hz), 3.62 (3H, s), 3.73 (1H, d, J = 11.1 Hz), 3.81-3.88 (2H, m), 3.89 (3H, s), 4.56 (1H, d, J = 13.9 Hz), 6.25 (1H, s), 6.64 (1H, d, J = 2.1 Hz), 7.00 (1H, dd, J = 7.2, 2.3 Hz), 7.15-7.39 (4H, m).

(3) Se añadió trietilamina (5.14 ml, 36.7 mmoles) a una solución de clorhidrato de hidroxiamina (2.55 g, 36.7 mmoles) en sulfóxido de dimetilo (40 ml), y la mezcla se agitó durante 30 minutos. Las sustancias insolubles se filtraron. Al filtrado se añadió 4-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]butanonitrilo (3.89 g, 7.35 mmoles) obtenido en el ejemplo 157-(2) y la mezcla se agitó a 80°C durante 6 horas. La solución de reacción se diluyó con acetato de etilo, y la capa orgánica se lavó con agua y una solución acuosa de cloruro de sodio, se secó sobre sulfato de magnesio y después se concentró bajo presión reducida para obtener acetato de 3-[(3R,5S)-3-[4-amino-4-(hidroxiimino)-butil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (4.33 g) como polvo

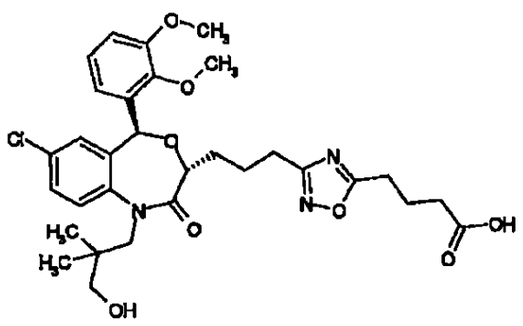
crudo.

(4) De conformidad con una manera similar a la del ejemplo 60, se obtuvo el compuesto del título a partir de acetato de 3-[(3R,5S)-3-[4-amino-4-(hidroxiimino)butil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo obtenido en el ejemplo 157-(3).

^{1}H-RMN ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 1.70-2.02 (4H, m), 2.66-2.78 (2H, m), 2.89 (2H, t, J = 7.2 Hz), 3.10-3.20 (3H, m), 3.36 (1H, d, J = 14.3 Hz), 3.57-3.66 (4H, m), 3.83-3.92 (4H, m), 4.45 (1H, d, J = 14.3 Hz), 6.12 (1H, s), 6.60 (1H, d, J = 2.3 Hz), 6.99 (1H, dd, J = 6.4, 3.4 Hz), 7.16-7.24 (2H, m), 7.30 (1H, d, J = 8.7 Hz), 7.36 (1H, dd, J = 8.7, 2.4 Hz).

EJEMPLO 158

Acido 4-(3-{3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]propil}-1,2,4-oxadiazol-5-il)butanoico

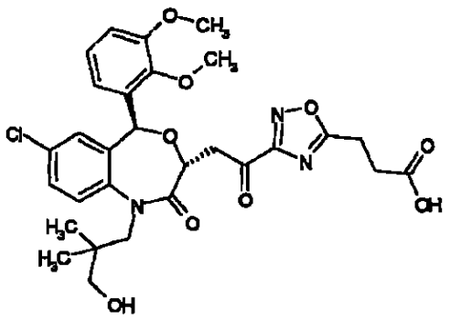


De conformidad con una manera similar a la del ejemplo 157, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 1.71-2.02 (4H, m), 2.08-2.20 (2H, m), 2.49 (2H, t, J = 7.2 Hz), 2.74 (2H, t, J = 6.4 Hz), 2.94 (2H, t, J = 7.3 Hz), 3.15 (1H, d, J = 12.1 Hz), 3.36 (1H, d, J = 14.3 Hz), 3.57-3.66 (4H, m), 3.83-3.92 (4H, m), 4.46 (1H, d, J = 14.3 Hz), 6.13 (1H, s), 6.60 (1H, d, J = 2.3 Hz), 6.99 (1H, dd, J = 6.8, 3.0 Hz), 7.16-7.24 (2H, m), 7.30 (1H, d, J = 8.7 Hz), 7.36 (1H, dd, J = 8.7, 2.1 Hz).

EJEMPLO 159

Acido 3-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}-1,2,4-oxadiazol-5-il)propiónico



(1) Trietilamina (4.05 ml, 28.9 mmoles) se añadió a una solución de clorhidrato de hidroxiamina (2.0 g, 5.78

mmoles) en sulfóxido de dimetilo (40 ml), y la mezcla se agitó durante 30 minutos. Las sustancias insolubles se filtraron. Al filtrado se añadió acetato de 3-[(3R,5S)-3-(2-{[ter-butil(dimetil)silil]oxi}-2-cianoetil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (3.73 g, 5.78 mmoles)obtenido en el ejemplo 115-(2) y la mezcla se agitó a 80°C durante 2.5 horas. La solución de reacción se diluyó con acetato de etilo, y la capa orgánica se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio y después se concentró bajo presión reducida para obtener acetato de 3-[(3R,5S)-3-{(3Z)-3-amino-2-{[ter-butil(dimetil) silil]oxi}-3-(hidroxiimino)propil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo como polvo crudo (4.07 g, 100%).

(2) Trietilamina (0.63 ml, 4.49 mmoles) y 4-cloro-4-oxobutanoato de etilo (0.47 ml, 3.29 mmoles) se añadieron gota a gota a una solución de acetato de 3-[(3R,5S)-3-[(3Z)-3-amino-2-[ter-butil(dimetil)silil]oxi}-3-(hidroxiimino)propil]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-2,3-dihidro-4,1-benzoxazepin-1(5H)-il]-2,2-dimetilpropilo (2.03 g, 2.99 mmoles) obtenido en el ejemplo 159-(1) en THF (20 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 4.5 horas. La solución de reacción se concentró bajo presión reducida, se añadió agua

(20 ml) al residuo, y la mezcla se calentó a reflujo durante 17.5 horas. Después de que la solución de reacción se diluyó con acetato de etilo, la capa orgánica se lavó con agua y una solución de cloruro acuosa saturada, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener 3-[3-(2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-1-{[ter-butil(dimetil)silil]oxi}etil)-1,2-4-5-oxadiazol-5-il]propionato de etilo (1.65 g, 70%).

^{1}H-RMN ($CDCl_3$) δ: -0.07-0.11 (6H, m), 0.69-0.89 (9H, m), 1.04 (3H, s), 1.09-1.15 (3H, m), 1.29-1.38 (3H, m), 2.09-2.14 (3H, m), 2.32-2.60 (2H, m), 2.85-2.95 (2H, m), 3.18-3.29 (2H, m), 3.61 (1H, d, J = 14.1 Hz), 3.68-3.72 (3H, m, J = 2.4 Hz), 3.80-3.87 (1H, m), 3.90-4.00 (4H, m), 4.15-4.33 (3H, m), 4.66 (1H, dd, J = 14.0, 8.2 Hz), 5.12-5.29 (1H, m), 6.34 (1H, d, J = 12.1 Hz), 6.72 (1H, dd, J = 10.3, 2.2 Hz), 7.03-7.11 (1H, m), 7.22-7.44 (4H, m).

(3) Un complejo de trifluoruro de boro-éter dietílico (0.53 ml, 4.19 mmoles) se añadió a una solución de 3-[3-(2-[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]-1-{[ter-butil(dimetil)silil]oxi}etil)-1,2-4-oxadiazol-

5-il]propionato de etilo (1.65 g, 2.09 mmoles) obtenida en el ejemplo 159-(2) en acetonitrilo (20 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 1 hora bajo enfriamiento con hielo. La solución de reacción se diluyó con acetato de etilo, y la capa orgánica se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio y después se concentró bajo presión reducida. A una solución del residuo en diclorometano (15 ml), se añadió trietilamina (0.87 ml, 6.23 ml) y una solución de un comlejo de trióxido de azufre-piridina (0.83 g, 5.19 mmoles) en DMSO (3.3 ml), que se preparó previamente, se añadió después gota a gota. La mezcla se agitó durante 20 horas. La solución de reacción se diluyó con acetato de etilo, y la capa orgánica se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio y después se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice para obtener 3-(3-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}-1,2,4-oxadiazol-5-il)propionato de etilo (1.05 g, 75%) como polvo crudo.

^{1}H-RMN ($CDCl_3$) δ: 0.94 (3H, s), 1.02 (3H, s), 1.25 (3H, t, J = 7.2 Hz), 2.02 (3H, s), 2.90 (2H, t, J = 7.3 Hz), 3.25 (2H, t, J = 7.3 Hz), 3.42 (1H, dd, J = 17.8, 5.4 Hz),

3.57 (1H, d, J = 14.3 Hz), 3.61 (3H, s), 3.73 (1H, d, J = 11.1 Hz), 3.80-3.93 (5 H, m), 4.16 (2H, q, J = 7.2 Hz), 4.54 (1H, d, J = 14.1 Hz), 4.62 (1H, dd, J = 8.0, 5.4 Hz), 6.28 (1H, s), 6.65 (1H, s), 6.98 (1H, dd, J= 6.4, 3.2 Hz), 7.13-7.21 (2H, m), 7.36 (2H, s).

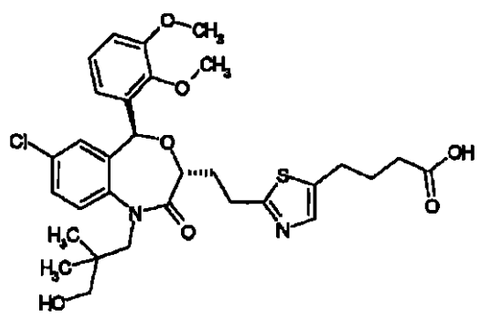
(4) Una solución acuosa 2 N de hidróxido de sodio (2.35 ml, 4.68 mmoles) se añadió a una solución de 3-(3-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}-1,2,4-oxadiazol-5-il)propionato de etilo (1.05 g, 1.562 mmoles) obtenida en el ejemplo 159-(3) en etanol (10 ml), y la mezcla se agitó durante 30 minutos. La solución de reacción se neutralizó con ácido clorhídrico acuoso 1 N, se extrajo con acetato de etilo, se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo se purificó por CLAR preparativa de Gilson para obtener ácido 3-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}-1,2,4-oxadiazol-5-il)propiónico (160 mg, 17%) como polvo.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.01-1.07 (3H, m), 2.98 (2H, t, J = 7.1 Hz), 3.16 (1H, d, J = 12.1 Hz), 3.25 (2H, t, J = 7.0 Hz), 3.37-3.48 (2H, m), 3.56-3.64 (4H, m),

3.74 (1H, d, J = 19.6 Hz), 3.82-3.96 (5 H, m), 4.43 (1H, d, J = 14.3 Hz), 4.61 (1H, dd, J = 8.3, 5.1 Hz), 6.16 (1H, s), 6.63 (1H, s), 6.99 (1H, dd, J = 7.2, 2.6 Hz), 7.13-7.23 (2H, m), 7.40 (2H, s).

EJEMPLO 160

Acido 4-(2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,3-tiazol-5-il)butanoico



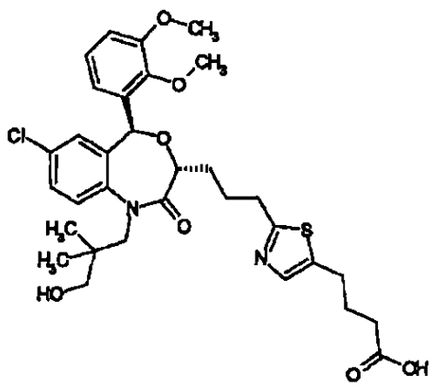
De conformidad con una manera similar a la del ejemplo 105, se obtuvo el compuesto del título

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 1.93 (2H, quintuplete, J = 7.5 Hz), 2.17-2.42 (4H, m), 3.616 (2H, t, J = 7.5 Hz), 3.622 (1H, d, J = 12.3 Hz), 3.82-3.94 (1H, m), 3.89 (3H, s), 4.45 (1H, d, J = 14.1 Hz), 6.15 (1H, s), 6.61 (1H, d, J = 2.7 Hz), 6.99 (1H, dd, J = 2.4, 7.2 Hz), 7.15-7.25 (2H, m), 7.30 (1H, d, J = 8.7 Hz), 7.35 (1H, dd, J = 2.7, 8.7 Hz).

704
713

EJEMPLO 161

Acido 4-(2-{3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]propil}-1,3-tiazol-5-il)butanoico

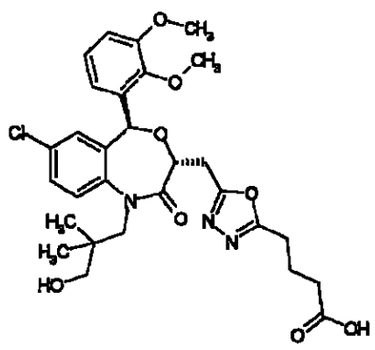


De conformidad con una manera similar a la del ejemplo 122, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 1.75-2.05 (6H, m), 2.39 (2H, t, J = 7.5 Hz), 2.84 (2H, J = 7.5 Hz), 2.90-3.01 (2H, m), 3.15 (1H, d, J = 12.0 Hz), 3.35 (1H, d, J = 14.4 Hz), 3.61 (3H, s), 3.62 (1H, d, J = 12.0 Hz), 3.80-3.92 (1H, m), 3.89 (3H, s), 4.46 (1H, d, J = 14.4 Hz), 6.13 (1H, s), 6.60 (1H, d, J = 2.4 Hz), 6.99 (1H, dd, J = 2.7, 7.2 Hz), 7.15-7.25 (2H, m), 7.30 (1H, d, J = 8.4 Hz), 7.31 (1H, s), 7.36 (1H, dd, J = 2.4, 8.4 Hz).

EJEMPLO 162

Acido 4-(5-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3,4-oxadiazol-2-il)butanoico

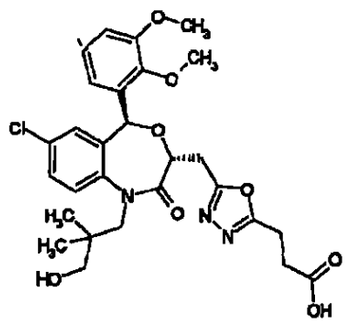


De conformidad con una manera similar a la del ejemplo 55, se obtuvo el compuesto del título. 1

^{1}H-RMN ($CDCl_3$) δ: 0.66 (3H, s), 1.05 (3H, s), 2.12 (2H, 5 quintuplete, J = 7.2 Hz), 2.49 (2H, t, J = 7.2 Hz), 2.93 (2H, J = 7.2 Hz), 3.17 (1H, d, J = 12.3 Hz), 3.29 (1H, dd, J = 6.6, 15.9 Hz), 3.41 (1H, d, J = 14.4 Hz), 3.47 (1H, dd, J = 6.6, 15.9 Hz), 3.614 (1H, d, J = 12.3 Hz), 3.6 (3H, s), 3.89 (3H, s), 4.46 (1H, d, J = 14.4 Hz), 4.51 (1H, t, J = 6.6 Hz), 6.21 (1H, s), 6.61 (1H, d, J= 2.1 Hz), 6.99 (1H, dd, J = 1.8, 7.8 Hz), 7.08 (1H, dd, J = 1.8, 7.8 Hz), 7.18 (1H, t, J = 7.8 Hz), 7.34-7.43 (2H, m).

EJEMPLO 163

Acido 3-(5-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3,4-oxadiazol-2-il)propiónico



(1) Piridina (0.067 ml, 0.83 mmoles) y anhídrido de ácido trifluorometansulfónico (0.13 ml, 0.79 mmoles) se añadieron a una solución de (4S)-4-(2-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-1,2,3,5-tetrahidro-2-oxo-4,1-benzoxazepin-3-il]acetil}hidrazino)-4-oxobutanoato de etilo (0.25 g, 0.38 mmoles) obtenida en el ejemplo 57-(1) en diclorometano (4 ml) a -10°C, y la mezcla se agitó durante 1 hora. Después de agitarse adicionalmente a 0°C durante 1 hora, una solución acuosa de bicarbonato de sodio (5 ml) se añadió a la misma y la mezcla se extrajo con diclorometano (80 ml). La capa orgánica se lavó con agua y una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio, y después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice [solvente de

revelado: hexano-acetato de etilo (3:2)] para obtener 3-(5-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3,4-oxadiazol-2-il)propionato de etilo (0.16 g, 0.25 mmoles, 66%) como polvo no cristalino incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (3H, s), 1.03 (3H, s), 1.26 (3H, t, J = 7.2 Hz), 2.03 (3H, s), 2.80-2.90 (2H, m), 3.14 (2H, t, J = 7.5 Hz), 3.29 (1H, dd, J = 7.2, 15.9 Hz), 3.43 (1H, dd, J = 6.6, 15.9 Hz), 3.55 (1H, d, J = 14.1 Hz), 3.62 (3H, s), 3.73 (1H, d, J = 10.8 Hz), 3.85 (1H, d, J = 10.8 Hz), 3.89 (3H, s), 4.16 (2H, q, J = 7.2 Hz), 4.42-4.93 (1H, m), 4.55 (1H, d, J = 14.1 Hz), 6.31 (1H, s), 6.63 (1H, d, J = 1.8 Hz), 6.98 (1H, dd, J = 1.5, 8.1 Hz), 7.07 (1H, dd, J = 1.5, 8.1), 7.18 (1H, t, J = 8.1 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.36 (1H, dd, J = 1.8, 8.4 Hz)

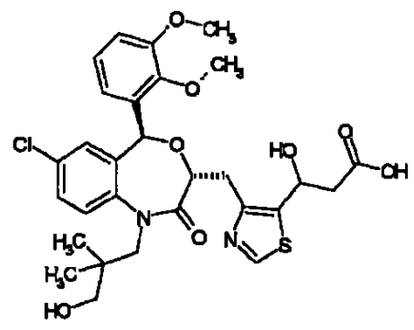
(2) Una mezcla de 3-(5-{[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3,4-oxadiazol-2-il)propionato de etilo (0.1 g, 0.16 mmoles) obtenida en el ejemplo 163-(1), una solución acuosa 1 N de hidróxido de sodio (0.6 ml) y etanol (5 ml) se agitó a temperatura ambiente durante 2 horas. La solución de reacción se concentró bajo presión reducida, se diluyó con agua (50 ml), y se lavó con éter dietílico (10 ml). La capa acuosa se

acidificó con ácido clorhídrico acuoso 1 N (1 ml) y después se extrajo con acetato de etilo (35 ml). La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio y después se concentró bajo presión reducida para obtener ácido 3-(5-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3,4-oxadiazol-2-il)propiónico (67 mg, 0.12 mmoles, 75%) como un cristal blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s), 1.04 (3H, s), 2.89 (2H, t, J = 7.5 Hz), 3.14 (2H, t, J = 7.5 Hz), 3.17 (1H, d, J = 11.7 Hz), 3.29 (1H, dd, J = 6.3, 15.9 Hz), 3.61 (3H, s), 3.62 (1H, d, J = 11.7 Hz), 3.89 (3H, s), 4.46 (1H, d, J = 14.4 Hz), 4.44-4.52 (1H, m), 6.20 (1H, s), 6.61 (1H, d, J = 1.8 Hz), 6.99 (1H, dd, J = 1.5, 8.1 Hz), 7.07 (1H, dd, J = 1.5, 8.1 Hz), 7.18 (1H, t, J = 8.1 Hz), 7.32-7.42 (2H, m).

EJEMPLO 164

Acido 3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)-3-hidroxipropiónico

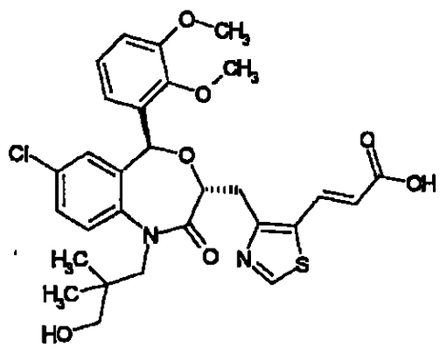


De conformidad con una manera similar a la del ejemplo 18, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.01 (3/2H, s), 1.04 (3/2H, s), 2.67-2.87 (2H, m), 3.10-3.22 (2H, m), 3.28-3.40 (2H, m), 3.49 (1H, dd, J = 7.8, 14.1 Hz), 3.62 (3H, s), 3.59-3.68 (1H, m), 3.88 (3/2H, s), 3.89 (3/2H, s), 4.37-4.54 (2H, m), 5.56 (1/2H, t, J = 5.7 Hz), 5.65 (1/2H, dd, J = 4.5, 8.7 Hz), 6.18 (1H, s), 6.52 (1/2H, d, J = 2.1 Hz), 6.57 (1/2H, d, J = 2.1 Hz), 6.86-7.04 (2H, m), 7.10-7.20 (1H, m), 7.25-7.36 (2H, m), 8.58 (1/2H, s), 8.61 (1/2H, s).

EJEMPLO 165

Acido (2E)-3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acrílico

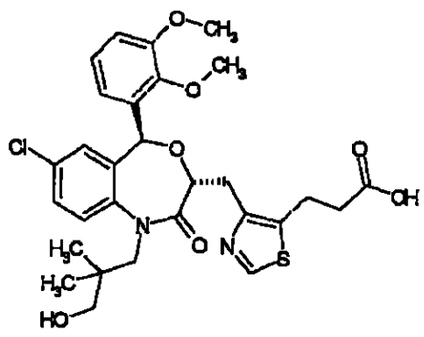


De conformidad con una manera similar a la del ejemplo 19, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.05 (3H, s), 3.19 (1H, d, J = 12.0 Hz), 3.32-3.51 (3H, m), 3.61 (3H, s), 3.67 (1H, d, J = 12.0 Hz), 3.87 (3H, s), 4.39 (1H, t, J = 6.0 Hz), 4.47 (1H, d, J = 14.4 Hz), 6.169 (1H, d, J = 15.6 Hz), 6.173 (1H, s), 6.54 (1H, d, J = 1.8 Hz), 6.85-6.97 (2H, m), 7.09 (1H, t, J = 8.1 Hz), 7.26-7.37 (2H, m), 8.03 (1H, d, J = 15.6 Hz), 8.67 (1H, s)

EJEMPLO 166

Acido 3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxıfenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepın-3-il]metil}-1,3-tiazol-5-il)propiónico

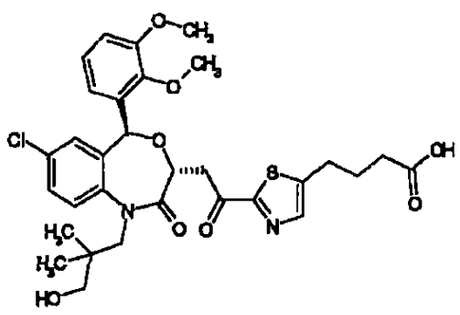


De conformidad con una manera similar a la del ejemplo 88, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.63 (3H, s), 1.04 (3H, s), 2.66 (2H, t, J = 7.5 Hz), 3.10-3.40 (6H, m), 3.61 (3H, s), 3.66 (1H, d, J = 12.0 Hz), 3.88 (3H, s), 4.38-4.46 (2H, m), 6.17 (1H, s), 6.53 (1H, d, J= 2.4 Hz), 6.90-7.00 (2H, m), 7.13 (1H, t, J = 7.8 Hz), 7.26-7.38 (2H, m), 8.52 (1H, s).

EJEMPLO 167

Acido 4-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}-1,3-tiazol-5-il)butanoico

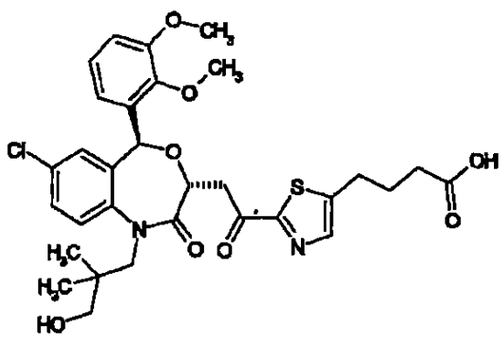


De conformidad con una manera similar a la del ejemplo 115, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.65 (3H, s}, 1.04 (3H, s), 1.95-2.10 (2H, m), 2.43 (1H, t, J = 7.2 Hz), 2.97 (2H, t, J = 7.2 Hz), 3.14 (1H, d, J = 12.0 Hz), 3.41 (1H, d, J = 14.1 Hz), 3.55 (1H, dd, J = 4.8, 18.3 Hz), 3.61 (3H, s), 3.63 (1H, d, J = 12.0 Hz), 3.89 (3H, s), 3.95 (1H, dd, J = 8.4, 18.3 Hz), 4.48 (1H, d, J = 14.1 Hz), 4.58 (1H, dd, J = 4.8, 8.4 Hz), 6.17 (1H, s), 6.62 (1H, s), 6.95-7.00 (1H, m), 7.13-7.21 (2H, m), 7.36-7.42 (2H, m), 7.70 (1H, s).

EJEMPLO 168

Acido 3-(5-{[(3R,5S)-7-cloro-5-(2,3-dimetilfenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}-2-tienil)propiónico



De conformidad con una manera similar a la del ejemplo 119, se obtuvo el compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 0.64 (3H, s), 1.04 (3H, s), 2.75 (2H, t, J = 7.2 Hz), 3.09-3.21 (3H, m), 3.27 (1H, dd, J = 4.5, 16.5 Hz), 3.40 (1H, d, J = 14.4 Hz), 3.58-3.74 (2H, m), 3.61 (3H, s), 3.89 (3H, s), 4.47 (1H, d, J = 14.4 Hz), 4.58 (1H, dd, J = 4.5, 8.4 Hz), 6.18 (1H, s), 6.62 (1H, s), 6.89 (1H, d, J = 3.6 Hz), 6.98 (1H, dd, J = 3.0, 7.2 Hz), 7.10-7.21 (2H, m), 7.35-7.42 (2H, m), 7.63 (1H, d, J = 3.6 Hz).

El agente para prevenir o tratar hiperlipemia de la presente invención se puede producir, por ejemplo, mediante las siguientes formulaciones.

En las siguientes formulaciones, ingredientes (aditivos) distintos a los ingredientes activos pueden ser

productos listados en Japanese Pharmacopoeia, Japanese Pharmaceutical Codex o Japanese Pharmaceutical Excipients.

EJEMPLO DE PREPARACION 1

Cápsula

(1) Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acético 10 mg

(2) Lactosa 90 mg

(3) Celulosa microcristalina 70 mg

(4) Estearato de magnesio 10 mg

Una cápsula 180 mg

(1), (2) y (3) y 1/2 de (4) se mezclan y después se granulan. Al mismo se añade el resto de (4) y todo se encapsula en una cápsula de gelatina.

715
724

EJEMPLO DE PREPARACION 2

Cápsula

(1) Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-neopentil-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]fietil}-1,3-tiazol-5-il)acético 10 mg

(2) Lactosa 90 mg

(3) Celulosa microcristalina 70 mg

(4) Estearato de magnesio 10 mg

Una cápsula 180 mg

(1), (2) y (3) y 1/2 de (4) se mezclan y después se granulan. Al mismo se añade el resto de (4) y todo se encapsula en una cápsula de gelatina.

EJEMPLO DE PREPARACION 3

Cápsula

(1) Acido 3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)propiónico 10 mg

(2) Lactosa 90 mg

(3) Celulosa microcristalina 70 mg

(4) Estearato de magnesio 10 mg

716
725.

Una cápsula 180 mg

(1), (2) y (3) y 1/2 de (4) se mezclan y después se granulan. Al mismo se añade el resto de (4) y todo se encapsula en una cápsula de gelatina.

EJEMPLO DE PREPARACION 4

Cápsula

(1) Acido (5-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)pentanoico 10 mg

(2) Lactosa 90 mg

(3) Celulosa microcristalina 70 mg

(4) Estearato de magnesio 10 mg

Una cápsula 180 mg

(1), (2) y (3) y 1/2 de (4) se mezclan y después se granulan. Al mismo se añade el resto de (4) y todo se encapsula en una cápsula de gelatina.

EJEMPLO DE PREPARACION 5

Tableta

(1) Acido (2-{[(3R,5S)-7-cloro-5-(2,3-

dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acético

	10 mg
(2) Lactosa	35 mg
(3) Almidón de maíz	150 mg
(4) Celulosa microcristalina	30 mg
(5) Estearato de magnesio	5 mg
Una tableta	230 mg

(1), (2), (3), 2/3 de (4) y 1/2 de (5) se mezclan y después se granulan. Al gránulo se añadió el resto de (4) y (5) y la mezcla se comprime en una tableta.

EJEMPLO DE PREPARACION 6

Tableta

(1) Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-neopentil-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acético

	10 mg
(2) Lactosa	35 mg
(3) almidón de maíz	150 mg
4) Celulosa microcristalina	30 mg
(5) Estearato de magnesio	5 mg
Una tableta	230 mg

(1), (2), (3), 2/3 de (4) y 1/2 de (5) se mezclan y después se granulan. Al gránulo se añade el resto de (4) y (5) y la mezcla se comprime en una tableta.

EJEMPLO DE PREPARACION 7

Tableta

(1) Acido 3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)propiónico	10 mg
(2) Lactosa	35 mg
(3) Almidón de maíz	150 mg
(4) Celulosa microcristalina	30 mg
(5) Estearato de magnesio	5 mg
Una tableta	230 mg

(1), (2), (3), 2/3 de (4) y 1/2 de (5) se mezclan y después se granulan. Al gránulo se añade el resto de (4) y (5) y la mezcla se comprime en una tableta.

EJEMPLO DE PREPARACION 8

Tableta

(1) Acido (5-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]fietil}-1,2,4-oxadiazol-5-il)pentanoico 10 mg

(2) Lactosa 35 mg

(3) Almidón de maíz 150 mg

(4) Celulosa microcristalina 30 mg

(5) Estearato de magnesio 5 mg

Una tableta 230 mg

(1), (2), (3), 213 de (4) y 112 de (5) se mezclan y después se granulan. Al gránulo se añade el resto de (4) y (5) y la mezcla se comprime en una tableta.

EJEMPLO DE PREPARACION 9

Inyección

(1) Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acético 10 mg

(2) Inositol 100 mg

(3) Alcohol bencílico 20 mg

Una ampolleta 130 mg

(1), (2) y (3) se disuelven en agua destilada para inyección por lo que el volumen total es de 2 ml y después se llena una ampolleta con el mismo. Todos los pasos se llevan a cabo bajo condición estéril.

EJEMPLO DE PREPARACION 10

Inyección

(1) Acido (2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-neopentil-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-tiazol-5-il)acético 10 mg

(2) Inositol 100 mg

(3) Alcohol bencílico 20 mg

Una ampolleta 130 mg

(1), (2) y (3) se disuelven en agua destilada para inyección por lo que el volumen total es de 2 ml y después se llena una ampolleta con el mismo. Todos los pasos se llevan a cabo bajo condición estéril.

EJEMPLO DE PREPARACION 11

Inyección

(1) Acido 3-(4-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}fenil)propiónico 10 mg

(2) Inositol 100 mg

(3) Alcohol bencílico 20 mg

Una ampolleta 130 mg

(1), (2) y (3) se disuelven en agua destilada para inyección por lo que el volumen total es de 2 ml y después se llena una ampolleta con el mismo. Todos los pasos se llevan a cabo bajo condición estéril.

EJEMPLO DE PREPARACION 12

Inyección

(1) Acido (5-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxi-fenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-il)pentanoico 10 mg

(2) Inositol 100 mg

(3) Alcohol bencílico 20 mg

Una ampolleta 130 mg

15 (1), (2) y (3) se disuelven en agua destilada para inyección por lo que el volumen total es de 2 ml y después se llena una ampolleta con el mismo. Todos los pasos se llevan a cabo bajo condición estéril.

EJEMPLO EXPERIMENTAL 1

Actividad inhibidora de escualeno sintasa

Método de medición

La actividad de escualeno sintasa se midió con el uso de una solución de enzima obtenida de conformidad con el siguiente método de preparación.

Es decir, una solución de enzima (proteína 0.8 µg) preparada de conformidad con el siguiente método de preparación se añadió a una solución (cantidad total de 50 µl) que contenía 5 µM [1-3H] de farnesil pirofosfato (actividad específica de 25 µCi/mol), NADPH 1 mM (nicotinamida adenina dinucleótido fosfato de tipo reducido), 5 mM de $MgCl_2$, 6 mM de glutation, 100 mM de regulador de pH de fosfato de potasio (pH7.4) y un fármaco de prueba (añadido como una solución acuosa o una solución de DMSO) y se hizo reaccionar a 37°C durante 45 minutos. Después de detener la reacción mediante la adición de 150 µl de solución mixta de cloroformo/metanol (1:2), se añadieron 50 µl de cloroformo y

50 µl de una solución 3N de hidróxido de sodio. Después, 50 µl de la capa de cloroformo (capa inferior) que contiene el producto de reacción cuyo componente principal era escualeno se mezcló con 3 ml de un escintilador de líquidos basado en tolueno y su radioactividad se midió con un contador de escintilación de líquidos.

La actividad inhibidora de escualeno sintasa se expresó como la concentración del fármaco de prueba requerida para inhibir 50% de radioactividad incorporada en la capa de cloroformo (CI_{50}, concentración molar (M)). Todos los compuestos descritos en los ejemplos mostraron actividad inhibidora de síntesis de escualeno potente que tenia CI_{50} de 1 µM o menor.

Preparación de una solución de enzima humana

Células de cáncer de hígado humano HepG2 (aproximadamente $1x10^9$ células) obtenidas al cultivar en medio de Eagle modificado por Dulbecco que contenía 10% de suero de bovino fetal (37°C en presencia de 5% de CO_2) se suspendió en 10 ml de un regulador de pH enfriado con hielo [regulador de pH de 100 mM de fosfato de potasio (pH7.4), 30 mM de nicotinamida, 2.5 mM de $MgCl_2$], se alteró por sonicación (30 segundos, dos veces) y después se centrifugó a 10000 x g durante 20 minutos (4°C). El sobrenadante

resultante se centrifugó después a 105000 x g durante 90 minutos (4°C). El precipitado se suspendió en un regulador de pH de 100 mM de fosfato de potasio enfriado con hielo (pH7.4) y después se centrifugó a 105000 x g durante 90 minutos (4°C). El precipitado se suspendió en un regulador de pH de 100 mM de fosfato de potasio enfriado con hielo (pH7.4) (concentración de proteína de aproximadamente 4 mg/ml). Esta suspensión se usó como una solución de enzima.

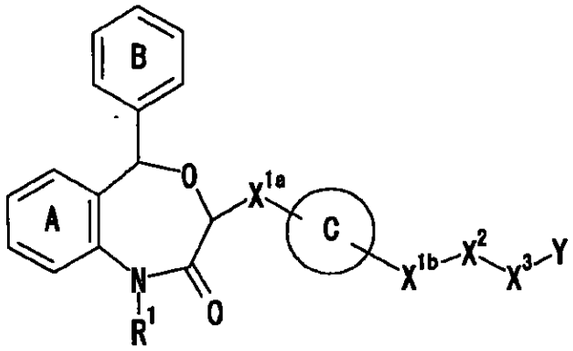
Como se ve a partir de los resultados anteriores, el compuesto de la presente invención tiene actividad inhibidora de escualeno sintasa superior.

Campo de aplicación industrial

Puesto que el compuesto de la presente invención tiene actividad inhibidora de escualeno sintasa, actividad reductora de colesterol y actividad reductora de triglicéridos y tiene alta selectividad para transición a un órgano objetivo y un margen de seguridad amplio, es útil como un agente para prevenir o tratar hiperlipemia como un agente reductor de lípidos y también es útil para prevenir o tratar arterioesclerosis.

REIVINDICACIONES

1. Un compuesto representado por la fórmula [1]:



caracterizado porque el anillo A y el anillo B representan cada uno un anillo de benceno opcionalmente sustituido, el anillo C representa un anillo aromático opcionalmente sustituido adicional, R^1 representa un grupo alquilo inferior opcionalmente sustituido con un grupo hidroxilo opcionalmente sustituido, X^{1a} representa un enlace o alquileno inferior opcionalmente sustituido, X^{1b} representa un enlace o alquileno inferior opcionalmente sustituido, X^2 representa un enlace, -O- o -S-, X^3 representa un enlace o un grupo hidrocarburo divalente opcionalmente sustituido, e Y representa un grupo carboxilo opcionalmente esterificado o amidado, o una sal del mismo.

2. El compuesto de conformidad con la reivindicación 1, caracterizado porque X^{1b} es un enlace e Y es un grupo carboxilo opcionalmente esterificado.

3. El compuesto de conformidad con la reivindicación 1, caracterizado porque el anillo A es un anillo de benceno sustituido con átomo(s) de halógeno.

4. El compuesto de conformidad con la reivindicación 1, caracterizado porque el anillo B es un anillo de benceno sustituido con grupo(s) alcoxi inferior.

5. El compuesto de conformidad con la reivindicación 1, caracterizado porque el anillo C es un anillo heterocíclico aromático monocíclico opcionalmente sustituido adicional.

6. El compuesto de conformidad con la reivindicación 1, caracterizado porque el anillo C es un anillo de benceno opcionalmente sustituido adicional.

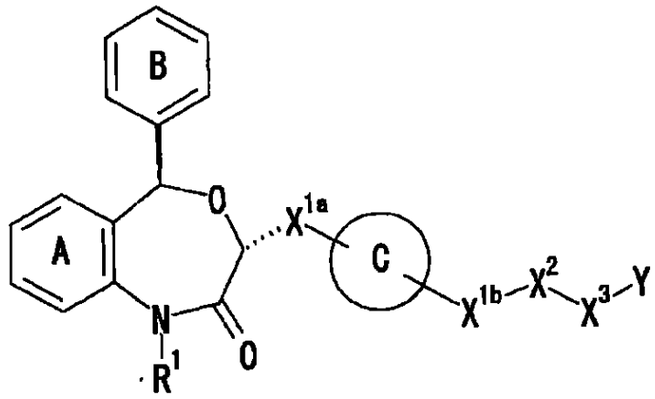
7. El compuesto de conformidad con la reivindicación 1, caracterizado porque el anillo C es un anillo aromático opcionalmente sustituido adicional que no tiene átomo de hidrógeno que puede ser desprotonado.

8. El compuesto de conformidad con la reivindicación 1, caracterizado porque X^{1a} es alquileno de C_{1-3}.

9. El compuesto de conformidad con la reivindicación 1, caracterizado porque X^2 es un enlace.

10. El compuesto de conformidad con la reivindicación 1, caracterizado porque X^3 es alquileno de C_{1-4}.

11. El compuesto de conformidad con la reivindicación 1, caracterizado porque la fórmula [I] es la fórmula [Ia]:



en donde los símbolos respectivos son como se definen en la reivindicación 1.

12. Acido 3-(2-{3-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]propil}-1,3-tiazol-5-il)propiónico, ácido 3-(2-{2-[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]etil}-1,3-tiazol-4-il)propiónico, o una sal de los mismos;

13. Acido 3-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(3-hidroxi-2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)propiónico, ácido 2-(2-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-isobutil-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,3-oxazol-5-il)acético, o una sal de los mismos.

14. Acido 5-(3-{[(3R,5S)-7-cloro-5-(2,3-dimetoxifenil)-1-(2,2-dimetilpropil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]metil}-1,2,4-oxadiazol-5-

ıl)pentanoıco, ácıdo 5-(3-{[(3R,5S)-7-cloro-5-(2,3-dımetoxıfenıl)-1-(3-hıdroxı-2,2-dımetılpropıl)-2-oxo-1,2,3,5-tetrahıdro-4,1-benzoxazepın-3-ıl]metıl}-1,2,4-oxadıazol-5-ıl)pentanoıco, ácıdo 5-(3-{[(3R,5S)-1-(3-acetoxı-2,2-dımetılpropıl)-7-cloro-5-(2,3-dımetoxıfenıl)-2-oxo-1,2,3,5-tetrahıdro-4,1-benzoxazepın-3-ıl]metıl}-1,2,4-oxadıazol-5-ıl)pentanoıco, o una sal de los mismos

15 Un profármaco del compuesto de conformidad con la reivindicación 1

16 Una medicina caracterizado porque comprende el compuesto de conformidad con la reivindicación 1 o un profármaco del mismo

17 Una medicina caracterizada porque comprende una combinación del compuesto de conformidad con la reivindicación 1 o un profármaco del mismo y un agente reductor de colesterol

18 La medicina de conformidad con la reivindicación 16 ó 17, caracterizada porque es un inhibidor de escualeno sintasa

19 La medicina de conformidad con la reivindicación 16 ó 17, caracterizada porque es un agente reductor de triglicéridos

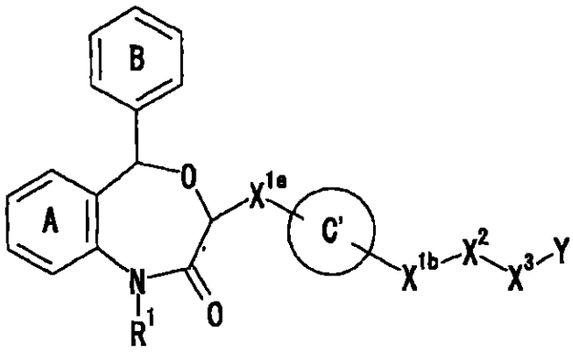
20 La medicina de conformidad con la reivindicación 16 ó 17, caracterizada porque es un agente reductor de lípidos

21 La medicina de conformidad con la reivindicación 16 ó 17, caracterizada porque es un agente para prevenir o tratar hiperlipemia

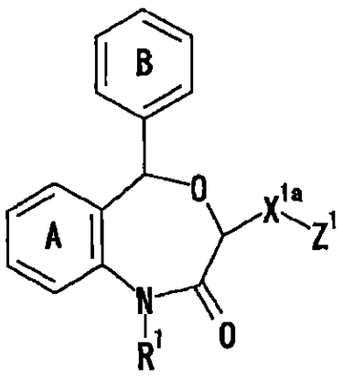
22 La medicina de conformidad con la reivindicación 16 ó 17, caracterizada porque es un agente elevador del nivel de colesterol-

lipoproteína de alta densidad.

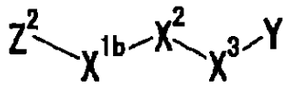
23. Un procedimiento para preparar un compuesto representado por la fórmula [I']:



caracterizado porque el anillo C' representa un anillo heterocíclico aromático opcionalmente sustituido adicional y otros símbolos son como se define en la reivindicación 1, o una sal del mismo, que comprende hacer reaccionar un compuesto representado por la fórmula:



en donde Z^1 representa un grupo funcional implicado en una reacción formadora de anillo heterocíclico aromático y otros símbolos son como se define en la reivindicación 1, o una sal del mismo, con un compuesto representado por la fórmula:



en donde Z^2 representa un grupo funcional implicado en una reacción formadora de anillo heterocíclico aromático y otros símbolos que se definen en la reivindicación 1, o una sal del mismo.

24. Un método para inhibir escualeno sintasa en un mamífero, caracterizado porque comprende administrar una cantidad efectiva del compuesto de conformidad con la reivindicación 1 o un profármaco del mismo al mamífero.

25. Un método para reducir el nivel de triglicéridos en un mamífero caracterizado porque comprende administrar una cantidad efectiva del compuesto de conformidad con la reivindicación 1 o un profármaco del mismo al mamífero.

26. Un método para reducir el nivel de lípidos en un mamífero, caracterizado porque comprende administrar una cantidad efectiva del compuesto de conformidad con la reivindicación 1 o un profármaco del mismo al mamífero.

27. Un método para prevenir o tratar hiperlipemia en un mamífero, caracterizado porque comprende administrar una cantidad efectiva del compuesto de conformidad con la reivindicación 1 o un profármaco del mismo al mamífero

28. Un método para elevar el nivel de colesterol-

lipoproteína de alta densidad en un mamífero, caracterizado poque comprende administrar una cantidad efectiva del compuesto de conformidad con la reivindicación 1 o un profármaco del mismo al mamífero.

29. El uso del compuesto de conformidad con la reivindicación 1 o un profármaco para la fabricación de un inhibidor de escualeno sintasa.

30. El uso del compuesto de conformidad con la reivindicación 1 o un profármaco del mismo para la fabricación de un agente reductor de triglicéridos.

31. El uso del compuesto de conformidad con la reivindicación 1 o un profármaco del mismo para la fabricación de un agente reductor de lípidos.

32. El uso del compuesto de conformidad con la reivindicación 1 o un profármaco del mismo para la fabricación de un agente para prevenir o tratar hiperlipemia.

33. El uso del compuesto de conformidad con la reivindicación 1 o un profármaco del mismo para la fabricación de un agente elevador del nivel de colesterol-lipoproteína de alta densidad.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2004/011293

A. CLASSIFICATION OF SUBJECT MATTER
Int Cl[7] C07D267/14, 417/06, 413/06, A61K31/553, 31/427, 31/4245, 45/00, A61P43/00, 3/06, 3/00, 13/12, 9/10, 9/06, 9/04, 7/00, 9/12, 3/10, 19/10, 1/18, 5/14, 25/28, 19/00, 21/00
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)
Int Cl[7] C07D267/14, 417/06, 413/06, A61K31/553, 31/427, 31/4245, 45/00, A61P43/00, 3/06, 3/00, 13/12, 9/10, 9/06, 9/04, 7/00, 9/12, 3/10, 19/10, 1/18, 5/14, 25/28, 19/00, 21/00

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 practicable, search terms used)
REGISTRY(STN), CAPLUS(STN), CAOLD(STN)

C DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	JP 9-136880 A (Takeda Chemical Industries, Ltd), 27 May, 1997 (27 05 97), Full text & WO 97/10224 A1 & CA 2231052 A & AU 9669442 A1 & EP 862562 A1 & CN 1196052 A & JP 2001-97963 A & EP 1097928 A1 & ZA 9702134 A & US 6110909 A & US 6613761 B1 & US 2004/072819 A1	1-23,29-33
Y	JP 7-267939 A (Takeda Chemical Industries, Ltd), 17 October, 1995 (17 10 95), Full text & WO 95/21834 A1 & AU 9515898 A1 & BR 9501469 A	1-23,29-33

☒ Further documents are listed in the continuation of Box C ☐ See patent family annex.

* Special categories of cited documents
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October, 2004 (14 10 04)	02 November, 2004 (02 11 04)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No	Telephone No

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2004/011293

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	JP 10-59953 A (Pfizer Inc.), 03 March, 1998 (03.03.98), Full text & EP 814080 A1 & uS 5965553 A & CA 2208174 A	1-23,29-33
Y	JP 2002-205956 A (Takeda Chemical Industries, Ltd.), 23 July, 2002 (23.07.02), Full text & WO 02/38180 A1 & EP 1332763 A1 & US 2004/063750 A1	22,33

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742

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2004/011293

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos: 24-28
because they relate to subject matter not required to be searched by this Authority, namely:
The inventions as set forth in claims 24 to 28 pertain to methods for treatment of the human body by therapy.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

受付 17.2.24 青山特許事務所

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To.

KAWAMIYA, Osamu
Aoyama & Partners, IMP Building
3-7, Shiromi 1-chome, Chuo-ku
Osaka-shi, Osaka 5400001
Japan

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 16 February 2005 (16.02.2005)	
Applicant's or agent's file reference 664638	**IMPORTANT NOTIFICATION**
International application No. PCT/JP2004/011293	**International filing date** (day/month/year) 30 July 2004 (30.07.2004)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
TAKEDA CHEMICAL INDUSTRIES, LTD. 1-1, Doshomachi 4-Chome, Chuo-ku Osaka-shi, Osaka 5410045 Japan	JP	JP
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
TAKEDA PHARMACEUTICAL COMPANY LIMITED 1-1, Doshomachi 4-Chome, Chuo-ku Osaka-shi, Osaka 5410045 Japan	JP	JP
	Telephone No	
	Facsimile No	
	Teleprinter No.	

3. Further observations, if necessary

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Denis RAMEN (Fax 338 7010)
Facsimile No (41-22) 338 70.10	Telephone No. (41-22) 338 9304

Form PCT/IB/308 (March 1994)

908604085

特許協力条約

SE RETIRA FOLIO 135 PARA PUBLICACIÓN./

744

Industria y Comercio
SUPERINTENDENCIA

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

Royal Technologies S.A.

Item		Expediente No 06009548. No de unidades	No de Folio √
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO	1	✓
10	OTROS		

Observaciones:

arte final

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO(COPIA
Radicacion : 06009548 000000000 Folios: 737
Fecha (AMD): 2006-02-01 17:21:32
Tramite : 011 PCT-PATENT 378 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

745

SUPERINDUSTRIA Y COMERCIO
Radicacion : 06009548 00000000 Folios: 737
Fecha (AMD): 2006-02-01 17:21:32
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 06 - 4,673
FECHA : ENERO 23 DE 2006

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	36494409	23/01/2006	36,366,160.00

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

NT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1	TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
			TOTAL : $	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cdo 14656-891-007-1

738

746

SUPERINDUSTRIA Y COMERCIO
Radicacion 06009548 00000000 Folios 737
Fecha (AMD) 2006-02-01 17 21 32
Tramite 011 PCT-PATENT 378 FASE NACI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

Industria y Comercio

SUPERINTENDI

SUPERINDUSTRIA Y COMERCIO(COPIA)
Idicacion 06009548 00390000 Folios 737
Fcha (AMD) 2006 02 01 17 21 32
Tramite 011 PCT PATENT 378 FASE NACI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

PCT

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN (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 se presenta la solicitud	( )	(X)
Descripción de la invención	( )	(X)
Dibujos de ser estos pertinentes	( )	(X)
Comprobante de Pago de las tasas establecidas	( )	(X)
COMPLETA (X) INCOMPLETA ( )	( )	( )
DISEÑO INDUSTRIAL ( )		
Indicación de que se solicita el registro de Diseño Industrial	( )	( )
Datos de identificación del solicitante o de la persona que se 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 Diseño Industrial	( )	( )
Datos de identificación del solicitante o de la persona que se presenta la solicitud	( )	( )
Representación gráfica del Esquema Trazado	( )	( )
Comprobante de Pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )

Firma Responsable _____

Fecha _____

739
747

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá
2020

Doctor(a)
FERRERO EMILIO
Apoderado(a) y/o Representante de
TAKEDA PHARMACEUTICAL COMPANY LIMITED

REFERENCIA	Radicación No	6 9548
	Solicitud internacional	JP2004/011293
	Fecha inicio fase nacional	01/03/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No	3829

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que

1 La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante (Art 26-k) Decisión 486

2 El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente (Regla 4 3 PCT, Art 26-27 D-486, Circular única 5 2 9)

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5 2, literal e), del capítulo quinto del título primero de la Circular Unica No 10 de 2001

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 31 MAR 2006
jramos