SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-163009- -00000-0000
Fecha: 2012-09-20 14:25:33 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 63

Industria y Comercio
SUPERINTENDENCIA
República de Colombia
Ministerio de Comercio, Industria y Turismo

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD DE

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No. _____

54. TITULO: **DERIVADO DE 1,3,4,8–TETRAHIDRO–2H–PIRIDO[1,2–a]PIRAZINA Y SU USO COMO INHIBIDOR DE LA INTEGRASA DEL VIH**

52. CLASIFICACION INTERNACIONAL: **C07D 471/04, A61K 31/4985, A61K 31/5377, A61P 31/18, A61P 43/00**

71. SOLICITANTE: **JAPAN TOBACCO INC.**

DOMICILIO: **2-1, Toranomon 2-chome, Minato-ku, Tokyo 105-8422 - JAPON**

74. APODERADO: **Dra. MARGARITA CASTELLANOS A.**

22. BOGOTA, D.C., 20 SET. 2012

Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación

DIRECCION DE NUEVAS CREACIONES
SOLICITUD FASE NACIONAL - PCT

1	(12) TIPO DE SOLICITUD	X Patente de Invención X Capítulo I	___ Patente de Modelo de Utilidad ___ Capítulo II
2	DATOS SOLICITUD INTERNACIONAL PCT (86)		
	Solicitud Internacional No.	PCT/JP2011/054404	Fecha 25/02/2011
	Publicación Internacional No.	WO 2011/105590 A1	Fecha 01/09/2011
3	(54) TITULO DE LA INVENCION (200 caracteres o espacios máximos)		
	DERIVADO DE 1,3,4,8–TETRAHIDRO–2H–PIRIDO[1,2–a]PIRAZINA Y SU USO COMO INHIBIDOR DE LA INTEGRASA DEL VIH		
4	CLASIFICACION INTERNACIONAL (51) CIP		
	C07D 471/04, A61K 31/4985, A61K 31/5377, A61P 31/18, A61P 43/00		
5	(71) SOLICITANTE(S) ___ Esta persona también es inventor	Para datos adicionales utilizar hoja de información adicional	

APELLIDOS O RAZON SOCIAL	NOMBRE	IDENTIFICACION	TIPO
JAPAN TOBACCO INC.			

6	DATOS DEL SOLICITANTE		
	DIRECCION	2-1, Toranomon 2-chome, Minato-ku	No. TELEFONO
	CIUDAD	Tokyo 1058422	E-MAIL
	DEPARTAMENTO/ESTADO		NACIONALIDAD O
	PAIS DE RESIDENCIA	JAPON	LUGAR DE CONSTITUCION JAPON
7	(72) INVENTOR(ES)	Para datos adicionales utilizar hoja de información adicional	

	APELLIDOS	NOMBRES	NACIONALIDAD
1.	MIYAZAKI	Susumu	JAPONESA
2.	BESSHO	Yuki	JAPONESA
3.	ADACHI	Kaoru	JAPONESA
4.	KAWASHITA	Seiji	JAPONESA
5.	ISOSHIMA	Hirotaka	JAPONESA
6	OSHITA	Kengo	JAPONESA
7.	FUKUDA	Shunichi	JAPONESA

DIRECCION DE CORREO ELECTRONICO:

8 DATOS INVENTOR(ES)

	PAIS RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCION
1.	JAPON		Osaka 5691125	c/o Central Pharmaceutical Research Institute of Japan Tobacco Inc., 1-1, Murasaki-cho, Takatsuki-shi
2.	JAPON		Osaka 5691125	c/o Central Pharmaceutical Research Institute of Japan Tobacco Inc., 1-1, Murasaki-cho, Takatsuki-shi
3.	JAPON		Osaka 5691125	c/o Central Pharmaceutical Research Institute of Japan Tobacco Inc., 1-1, Murasaki-cho, Takatsuki-shi
4.	JAPON		Osaka 5691125	c/o Central Pharmaceutical Research Institute of Japan Tobacco Inc., 1-1, Murasaki-cho, Takatsuki-shi
5.	JAPON		Osaka 5691125	c/o Central Pharmaceutical Research Institute of Japan Tobacco Inc., 1-1, Murasaki-cho, Takatsuki-shi
6.	JAPON		Osaka 5691125	c/o Central Pharmaceutical Research Institute of Japan Tobacco Inc., 1-1, Murasaki-cho, Takatsuki-shi
7.	JAPON		Osaka 5691125	c/o Central Pharmaceutical Research Institute of Japan Tobacco Inc., 1-1, Murasaki-cho, Takatsuki-shi

OTRO(S) SOLICITANTE(S) Y/U OTRO(S) INVENTOR(ES)

___ Los demás solicitantes y/o demás inventores se indican en una hoja a continuación

9 (74) ___ REPRESENTANTE X APODERADO

APELLIDOS	NOMBRES	IDENTIFICACION
CASTELLANOS ABONDANO	MARGARITA	C.C. 39.779.654 T.P. 70.819

DIRECCION	Calle 94A No. 7A-09	No. TELEFONO	7560770
		E-MAIL	info@castellanosyco.co
CIUDAD	BOGOTA	No. DE PROTOCOLO	
PAIS	COLOMBIA	EN LA OFICINA	

10 **(30) DECLARACIONES DE PRIORIDAD** ___X___ SI _____ NO

(33) PAIS DE ORIGEN	CODIGO PAIS	(31) NUMERO	(32) FECHA (AAA/MM/DD)
1. JAPON	JP	043567/2010	2010/02/26
2. ESTADOS UNIDOS	US	61/339,729	2010/03/09
3.			

11 **DECLARACION SOBRE USO DE RECURSOS GENETICOS O BIOLOGICOS**

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de recursos genéticos o biológicos de los que cualquiera de los paises miembros de la Comunidad Andina es país de origen.

_____ SI ___X___ NO

NOTA: En caso afirmativo deberá anexar copia del contrato de acceso de recursos genéticos o productos derivados, o certificado o número de registro expedido por la Autoridad competente.

12 **DECLARACION SOBRE USO DE CONOCIMIENTOS TRADICIONALES**

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de conocimientos tradicionales de comunidades indígenas, afroamericanas o locales de países miembros de la Comunidad Andina.

_____ SI ___X___ NO

NOTA: En caso afirmativo deberá anexar la licencia o autorización de uso de conocimiento tradicional, o certificado, o número de registro expedido por la Autoridad competente.

13 **REDUCCION DE TASAS**

Declaro que carezco de medios económicos para presentar la solicitud de patente

_____ SI ___X___ NO

NOTA: En caso de ser persona natural y carecer de medios económicos, y por lo tanto, aplique la reducción de tasas a que se refiere la resolución vigente en tarifas, debe firmar la presente solicitud bajo la gravedad de juramento.

Micro, pequeñas y medianas empresas	Universidades públicas o privadas	Entidades sin animo de lucro
_____ Copia simple de la declaración de renta del año inmediatamente anterior, o en su defecto prueba documental idónea. _____ Documento de constancia de cumplimiento con lo establecido en la ley 905 de 2004.	_____ Copia acto de reconocimiento institucional emitido por el Ministerio de Educación. Acreditación Colciencias.	_____ Copia de registro vigente en Cámara de Comercio. _____ Hoja de información complementaria. _____ Otros, especificar.

14 **AUTORIZACION DE NOTIFICACION EN LINEA** _____ SI ___X___ NO

Manifiesto que he leído y entendido perfectamente los términos y condiciones de uso de medios electrónicos para las notificaciones en linea a través de Internet de los actos administrativos proferidos por la Superintendencia de Industria y Comercio que deber ser notificados personalmente y, en consecuencia, autorizo el servicio de notificación a través de internet.

14	**COMPROBANTE DE PAGO O PAGO ELECTRONICO**	**N° 12-0092594, 12-0092602**	**Fecha: Septiembre 10 de 2012**

15 **FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL**
Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)

20 SET. 2012

MARGARITA CASTELLANOS ABONDANO - APODERADO

16 **ORDEN Y RELACION DE DOCUMENTOS QUE ACOMPAÑAN LA SOLICITUD**

Documentación Técnica
Solicitud Internacional en Castellano

1. ___X___ Descripción N° de folios: **323**
2. ___X___ Reivindicaciones N° de reivindicaciones: **42**
3. _____ Dibujos y/o figuras N° de folios:
4. ___X___ Resumen
5. _____ Certificado de depósito de material biológico si fuera el caso.
6. _____ Listado de secuencias de nucleótidos y/o aminoácios en forma digital si fuera el caso.
7. ___X___ Arte final 12 x 12
8. ___X___ Anexo formato digital.
   CD-R que contiene los siguientes archivos:
   * Texto en español de la descripción, reivindicaciones . resumen y figuras
   ** Texto de la publicación internacional

Documentación Jurídica

9. ___X___ Poderes, si fuera el caso.
10. ___X___ Documento que legalmente pruebe la cesión del inventor al solicitante o a su causante.
11. _____ Copia del contrato de acceso de recursos genéticos o productos derivados, certificado o número de registro, si fuera el caso.
12. _____ Copia de la licencia o autorización de Conocimientos Tradicionales, certificado o número de registro, si fuera el caso.
13. _____ Documento que acredita la existencia y representación legal, cuando el solicitante es persona jurídica.
14. ___X___ Comprobante de pago de la tasa de presentación de la solicitud.
15. _____ Comprobante de pago por reivindicación de prioridad
16. _____ Comprobante de pago de la tasa por concepto de excedente de palabras en la publicación.
17. ___X___ Comprobante de pago por reivindicación adicional a 10.

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0092594

Bogotá D.C., Septiembre 10 de 2012 - 15:43:56

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	462586832	10/09/2012	8.690.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	590.000.00	590.000.00
				$590.000.00

SON: **QUINIENTOS NOVENTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____
****

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-163009- -00000-0000

Fecha: 2012-09-20 14:25:33 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 63

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0092602

Bogotá D.C., Septiembre 10 de 2012 - 15:43:56

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	462586832	10/09/2012	8.690.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
32	50005-01-01 SOLICITUDES	1607 REIVINDICACION UNITARIA ADICIONAL A LAS 10 INICICIALES	30.000.00	960.000.00
				$960.000.00

SON: **NOVECIENTOS SESENTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-*********-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-163009- -00000-0000

Fecha: 2012-09-20 14:25:33 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 63

PODER

El (los) suscrito (s) JAPAN TOBACCO INC.

domiciliado (s) en 2-1, Toranomon 2-chome, Minato-ku, Tokyo 105-8422 - JAPON

nombra(n) por el presente a **XIMENA CASTELLANOS A.** y/o **MARGARITA CASTELLANOS A.** abogadas con oficinas en la Carrera 9 No. 93-09, Bogotá - Colombia para

y para obtener la protección de mi (nuestra) propiedad industrial y con este fin autorizamos a dichos apoderados para que nos representen ante cualesquiera autoridades o personas de los órdenes administrativo, contencioso-administrativo y judicial en todo lo relacionado con los siguientes actos y gestiones:

a) Obtención de patentes de invención , modelos y dibujos industriales; registro de marcas de fábrica, de servicio, colectivas o defensivas y de denominaciones de origen; depósito de nombres y enseñas comerciales; su renovación prórroga, inscripción de traspaso y cambio de nombre o domicilio, cancelación voluntaria y el registro de licencias de uso de esos derechos; b) Para la obtención de Registros Sanitarios; c) Acciones de oposición, observación, cancelación, nulidad, medidas cautelares y en general los juicios civiles, penales, administrativos o contencioso-administrativos que promovamos o se nos promuevan, pudiendo en todos los actos y gestiones arriba determinados sustituir éste mandato, transigir, desistir, recibir, cancelar, renunciar, aceptar notificaciones y nombrar apoderados judiciales y extrajudiciales.

Dado y firmado hoy 7 de Junio de 2004

en Tokyo, JAPON

Por Teruo DAITO

(Notary should execute on other side)
(Consular legalization necessary)

POWER OF ATTORNEY

I (we) the undersigned Japan Tobacco Inc.

of 2-1, Toranomon 2-chome, Minato-ku, Tokyo 105-8422 Japan

hereby grant(s) Power of Attorney to **XIMENA CASTELLANOS A.** and/or **MARGARITA CASTELLANOS A.** attorneys residing at Carrera 9 No. 93-09 Bogotá - COLOMBIA to

and to obtain the protection of my (our) industrial property, for which purpose we authorize the said attorneys to represent us before any authorities or persons , specially those, administrative contentious and judicial, in all matters concerning the following :

a) Obtention of patents, models and designs; registration of trademarks, service, collective and defensive marks, and of designations of origin; the deposit of commercial names and ensigns; its renewal , extension, recordal of assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rigths; b) For de obtention of Sanitary Registrations; c) Actions of opposition, cancellation, nullity, infringement, granting of licenses; and in general the civil, criminal and administrative suits related to those rigths; actions and suits instituted by us or against us; and that in all the above matters they may substitute this Power of Attorney, compromise, desist, cancel, receive, renounce, accept notifications and appoint attorneys in fact, in or out of Court .

Given and signed this June 7, 2004

in Tokyo - JAPAN

By Japan Tobacco Inc.

Teruo DAITO, Patent Attorney
General Manager,
Patent Information Dept.

(Notary should execute on other side)
(Consular legalization necessary)

ALVARO CASTELLANOS M. & CIA.
ABOGADOS COLOMBIA

Carrera 9 No. 93-09 - P.O. Box 6349 - Bogotá, Colombia.
Tels.: (571) 610 7420 /60 / 80 - Fax. (571) 610 0706 - e-mail acastell@impsat.net.co

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: **JAPAN**

This public document

2. has been signed by Katsuyuki YAMAGUCHI
3. acting in the capacity of Notary Public of the Osaka Legal Affairs Bureau
4. bears the seal/stamp of Katsuyuki YAMAGUCHI, Notary Public

Certified

5. at **Osaka**
6. JUN. 14. 2004
7. by **the Ministry of Foreign Affairs**
8. No. 02041
9. Seal/stamp:
10. Signature:

Tsutomu HIGUCHI
For the Minister for Foreign Affairs

認証登簿平成１６年第100号

嘱託人大東輝雄は、本公証人の面前で、別紙編綴の書面に署名した。

よって、これを認証する。

平成１６年３月３１日、本職の役場において。

大阪府高槻市芥川町１丁目１５番１８号(ミドリ芥川ビル内)

大阪法務局所属

公証人　山口勝之

Registerd No100(2004)

NOTARIAL CERTIFICATE

This is to certify that Teruo DAITO signed the attached document in my very presence on this 31st day of March 2004.

Katsuyuki Yamaguchi

Katsuyuki Yamaguchi
Notary, attached to
Osaka Legal affairs Bureau
15-18,1-chome,Akutagawa-cho,
Takatsuki-shi,Osaka,Japan.

OSAKA LEGAL AFFAIRS BUREAU
NOTARY
15-18,(Midori Akutagawa Bldg.)1-chome
Akutagawa-cho,Takatsuki-shi,Osaka,Japan

大阪法務局所属　公証人役場

証明書

東京都港区虎ノ門二丁目２番１号を本店所在地とする日本国法人日本たばこ産業株式会社の代表取締役社長である私 本田勝彦 は、該法人を代表して知的財産権に係わる書類を署名作成する権限を有するものであることをここに宣言し、これをもって、２００４年３月３１日当時、該法人の医薬総合研究所特許情報室長職にあった大東輝雄　氏が、代理人に指名され、該法人名義にて外国に提出する特許、実用新案登録の出願等手続に要する願書、委任状、譲渡書、授権書、申請書、請求書、その他を含む関係書類について該法人を代表して署名、押印、作成する権限を有していたものであることを証明する。

２００４年６月７日

日本たばこ産業株式会社

代表取締役社長　本田　勝彦

CERTIFICATE

I, KATSUHIKO HONDA, President and Chief Executive Officer of JAPAN TOBACCO INC., a Japanese corporation located at 2-1, TORANOMON 2-CHOME, MINATO-KU, TOKYO 105-8422, JAPAN, hereby declare that I am authorized to sign and execute documents relating to intellectual property rights on behalf of the said corporation, and hereby certify that, as of March 31, 2004, Mr. TERUO DAITO was Director of Patent Information Dept. of Central Pharmaceutical Research Institute of the said corporation, was my proxy, and was authorized to sign and execute documents relating to intellectual property rights on behalf of the said corporation. Said documents include, but are not limited to, applications, powers of attorney, assignments, authorizations of agents, petitions and the like in connection with patent and utility model filed in foreign countries with the name of the said corporation.

Dated this 7 day of June , 2004,
JAPAN TOBACCO INC.

KATSUHIKO HONDA
President and Chief Executive Officer

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: **JAPAN**

This public document

2. has been signed by — Katsuyuki YAMAGUCHI
3. acting in the capacity of — Notary Public of the Osaka Legal Affairs Bureau
4. bears the seal/stamp of — Katsuyuki YAMAGUCHI, Notary Public

Certified

5. at **Osaka**
6. JUN. 14. 2004
7. by **the Ministry of Foreign Affairs**
8. No. 02042
9. Seal/stamp:
10. Signature:

Tsutomu HIGUCHI
For the Minister for Foreign Affairs

登簿番号平成１６年第１６８号

日本国法律に従い設立され、日本国東京都港区虎ノ門二丁目２番１号に所在する日本たばこ産業株式会社において、２００４年3月３１日当時、医薬総合研究所特許情報室長職にあった大東輝雄氏が、該法人名義で知的財産関係書類について該法人を代表して署名押印、作成する権限を有していたこと及び同氏が２００４年３月３１日、本職の面前で別紙書類に署名したことを証明する。

よって、ここにこれを認証する。

平成１６年６月８日、本職の役場において。

大阪府高槻市芥川町１丁目１５番１８号（ミドリ芥川ビル）

大阪法務局所属（高槻公証役場）

公証人　山口勝之

大阪法務局所属　公証人役場

Registration Book No.168 (2004)

NOTARIAL CERTIFICATE

This is to certify that :

1) Teruo Daito was Director of Patent Information Dept. of Central Pharmaceutical Reseearch Institute of JAPAN TOBACCO INC. ,a Japanese corporation of being legally constituted and in existance in accordance with the laws of Japan ,located at 2-1, Toranomon2-chome, Minato-ku, Tokyo 105-8422 Japan ,as of March 31,2004 and was authorized to sign and execute documents relating to intellectual property rights on behalf of the said corporation.

2) said Teruo Daito signed the attaced document in my presence on 31st day of March,2004.

IN TESTIMONY WHEREOF,I have hereto subscribed my name and affixed my seal of office.

On the 8th day of June,2004
at the Office of Notary Katsuyuki Yamaguchi

Katsuyuki Yamaguchi

OSAKA LEGAL AFFAIRS BUREAU
NOTARY
15-18,(Midori Akutagawa Bldg.)1-chome
Akutagawa-cho,Takatsuki-shi,Osaka,Japan

Katsuyuki Yamaguchi
Notary,attached to
Osaka Legal affairs Bureau,
15-18,1-chome,Akutagawacho,
Takatsuki-shi, Osaka,Japan.

総第 1558 号

証　　明

大阪法務局所属公証人　山口勝之

平成 16 年 3 月 31 日付

平成16年 登簿 第 100 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。

平成16年6月14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. 6. 14

Director of the Osake Legal Affairs Bureau

総第 1559 号

証　　明

大阪法務局所属公証人　山口勝之

平成 16年 6 月 8 日付

平成16年 登簿 第 168 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。

平成16年6月14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. 6.14

Director of the Osake Legal Affairs Bureau

----------TRADUCCION OFICIAL No. 04-0616----------

de un documento escrito en INGLES, el cual para su identificación lleva el sello de la Traductora e Intérprete Oficial, Res. 2755/68 y 01144/97 de Minjusticia, al igual que la presente.----------

(Anexo a un documento de poder otorgado por Japan Tobacco Inc.)

Registro No. 100 (2004)

CERTIFICADO NOTARIAL

La presente es para certificar que Teruo DAITO firmó el documento adjunto en mi propia presencia hoy día 31 de marzo de 2004.

(fdo) ilegible

Katsuyuki Yamaguchi

Notario adjunto a la Oficina de Asuntos Legales de Osaka – 15-18, 1-chome, Akutagawa-cho, Takatsuki-shi, Osaka, Japón

(Sello) Oficina de Asuntos Legales de Osaka

NOTARIO – 15-18 (Midori Akutagawa Bldg) 1-chome

Akutagawa-cho, Takatsuki-shi, Osaka, Japón

APOSTILLA

(Convención e La Haya del 5 de Octubre de 1961)

1. País: JAPON

Este documento público

2. ha sido firmado por Katsuyuki YAMAGUCHI
3. actuando en su carácter de Director de la Oficina de Asuntos legales de Osaka

DORA [illegible] DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
RES. 02[illegible]58 Y 01144/97 - MINJUSTICIA
REP. DE COLOMBIA

4. lleva el sello de Katsuyuki YAMAGUCHI, Notario Público

Certificado

5. en Osaka 6. el 14 de Junio 2004

7. por el Ministerio de Relaciones Exteriores

8. No. 02041

9. Sello: 10: Firma

(fdo) ilegible

Tsutomu HIGUCHI

Por el Ministro de Relaciones Exteriores.

(Sello del Ministerio de Relaciones Exteriores de Japón)

CERTIFICADO

Yo, KATSUHIKO HONDA, Presidente y Funcionario jefe Ejecutivo de JAPAN TOBACCO INC., una sociedad japonesa situada en 2-1, TORANOMON 2-CHOME, MINATO-KU, TOKYO 105-8422, JAPON, declaro por medio del presente que estoy autorizado para firmar y otorgar documentos relacionados con derechos de propiedad intelectual en nombre de dicha sociedad, y por medio del presente certifico que, a Marzo 31 de 2004, el señor TERUO DAITO era el Director del Departamento de Información de Patentes del Instituto Central de Investigaciones Farmacéuticas de dicha sociedad, era mi apoderado y estaba autorizad para firmar y otorgar documentos relacionados con derechos de propiedad intelectual en nombre de dicha sociedad. Dichos documentos incluyen, pero no se limitan a, solicitudes, poderes, cesiones, autorizaciones de agentes, peticiones y similar en relación con

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REP. DE COLOMBIA

patentes y modelos de utilidad presentados en países extranjeros con el nombre de dicha sociedad.

Dado hoy día 7 de Junio de 2004

JAPAN TOBACCO INC.

KATSUHIKO HONDA

Presidente y Funcionario Jefe Ejecutivo

Libro de Registro No. 168 (2004)

CERTIFICADO NOTARIAL

La presente es para certificar que:

1) Teruo Daito era el Director del departamento de Información de Patentes del Instituto Central de Investigaciones Farmacéuticas de JAPAN TOBACCO INC., una sociedad japonesa que están legalmente constituida y existe de acuerdo con las leyes del Japón, situada en 2-1, Toranomon 2-chome, Minato-ku, Tokio 105-8422 Japón, a Marzo 31 de 2004, y estaba autorizado para firmar y otorgar documentos relacionados con derechos de propiedad intelectual en nombre de dicha sociedad.
2) Dicho Tereuo Daito firmó el documento adjunto en mi propia presencia el día 31 de Marzo de 2004.

EN TESTIMONIO DE LO CUAL, he suscrito aquí mi nombre y he fijado mi sello de oficio.

El día 8 de Junio de 2004

En la Oficina del Notario Katsuyuki Yamaguchi

(fdo) ilegible

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Katsuyuki Yamaguchi

Notario adjunto a la Oficina de Asuntos Legales

De Osaka, 15-18, 1-chome, Akutagawacho

Takatsuki-shi, Osaka, Japón

(Sello) Oficina de Asuntos Legales de Osaka

NOTARIO – 15-18 (Midori Akutagawa Bldg) 1-chome

Akutagawa-cho, Takatsuki-shi, Osaka, Japón

CERTIFICADO 1558

La presente es para certificar que la firma que aparece anteriormente ha sido impuesta por Notario, debidamente autorizado y en ejercicio en Osaka, Japón y que el sello oficial que aparece en el mismo es auténtico.

Fecha: 04.6.14

Director de la Oficina de Asuntos Legales de Osaka

CERTIFICADO 1559

La presente es para certificar que la firma que aparece anteriormente ha sido impuesta por Notario, debidamente autorizado y en ejercicio en Osaka, Japón y que el sello oficial que aparece en el mismo es auténtico.

Fecha: 04.6.14

Director de la Oficina de Asuntos Legales de Osaka

APOSTILLA

(Convención e La Haya del 5 de Octubre de 1961)

5. País: JAPON

Este documento público

6. ha sido firmado por Katsuyuki YAMAGUCHI

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RES. 02785/08 Y 0144797 - MINJUSTICIA
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7. actuando en su carácter de Director de la Oficina de Asuntos legales de Osaka
8. lleva el sello de Katsuyuki YAMAGUCHI, Notario Público

Certificado

5. en Osaka 6. el 14 de Junio 2004
7. por el Ministerio de Relaciones Exteriores
8. No. 02042
9. Sello: 10: Firma

(fdo) ilegible

Tsutomu HIGUCHI

Por el Ministro de Relaciones Exteriores.

(Sello del Ministerio de Relaciones Exteriores de Japón)

Es traducción fiel y completa, a la cual me remito,

Bogotá, Junio 22, 2004.

DORA DUQUE DE BERNAL
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RES. 02755/68 Y 01144/97 - MINJUSTICIA
REP. DE COLOMBIA

3

EXTERIORES

041035

CUYA FIRMA APARECE EN EL
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LAS FUNCIONES INDICADAS

2004 JUN 24 A 11:23

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

P A T E N T S

CESION

El (los) suscrito (s)

Susumu MIYAZAKI
Yuki BESSHO
Kaoru ADACHI
Seiji KAWASHITA
Hirotaka ISOSHIMA
Kengo OSHITA
Shunichi FUKUDA

en consideración al pago de la suma de (.....), que he(mos) recibido, por el presente documento cedo (cedemos) a

Japan Tobacco Inc.

una compañía constituida de conformidad con las leyes de

con oficinas en

2-1, Toranomon 2-chome, Minato-ku, Tokyo 105-8422 Japón

todos los derechos y títulos sobre la invención denominada
DERIVADO DE 1,3,4,8-TETRAHIDRO-2H-PIRIDO(1,2-a) PIRAZINA Y SU USO COMO INHIBIDOR DE LA INTEGRASA DEL VIH
EL CESIONARIO firma también el presente y declara que acepta dicha cesión

Dado y firmado hoy 27 de Julio de 2012

en Osaka, JAPON

ASSIGNMENT

The undersigned

Susumu MIYAZAKI
Yuki BESSHO
Kaoru ADACHI
Seiji KAWASHITA
Hirotaka ISOSHIMA
Kengo OSHITA
Shunichi FUKUDA

in consideration of the sum of (.....), the receipt of which is hereby acknowledged, by these presents do sell, assign and transfer unto

Japan Tobacco Inc.

a corporation organized under the laws of Japan

having a place of business at

2-1, Toranomon 2-chome, Minato-ku, Tokyo 105-8422 Japan

all rights and title to the invention related to

1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZINE DERIVATIVE AND USE OF SAME AS HIV INTEGRASE INHIBITOR

THE ASSIGNEE signs these presents and declares that accepts the aforesaid assignment

Given an signed this July 27, 2012

in Osaka, Japan

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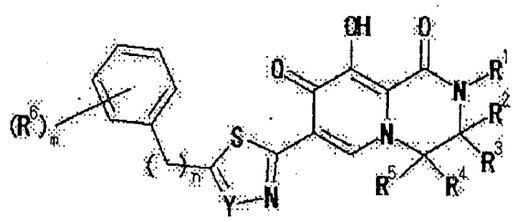
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(84) 指定国 (表示のない限り、全ての種類の広域保護が可能): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), ユーラシア (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI

[続葉有]

(54) Title: 1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZINE DERIVATIVE AND USE OF SAME AS HIV INTEGRASE INHIBITOR

(54) 発明の名称: １，３，４，８－テトラヒドロ－２Ｈ－ピリド［１，２－ａ］ピラジン誘導体及びそのＨＩＶインテグラーゼ阻害剤としての利用



[I]

(57) Abstract: Disclosed is a novel 1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrazine derivative, a pharmaceutically acceptable salt thereof or a solvate thereof, which is useful as an anti-HIV agent. Specifically disclosed is a compound represented by general formula (I), a pharmaceutically acceptable salt thereof or a solvate thereof. (In the formula, the symbols are as defined in the description.)

(57) 要約: 抗ＨＩＶ剤として有用な、新規１，３，４，８－テトラヒドロ－２Ｈ－ピリド［１，２－ａ］ピラジン誘導体又はその医薬上許容される塩、或いはその溶媒和物を提供する。 下記一般式［Ｉ］で表される化合物又はその医薬上許容される塩、或いはその溶媒和物に関する［式中、各記号は明細書中と同義である］。

WO 2011/105590 A1

(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

添付公開書類:

— 国際調査報告（条約第 21 条(3)）

— 明細書の別個の部分として表した配列リスト（規則 5.2(a)）

DESCRIPTION

Title of the Invention: 1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZINE DERIVATIVE AND USE OF SAME AS HIV INTEGRASE INHIBITOR

TECHNICAL FIELD

[0001]

The present invention relates to a novel 1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrazine derivative useful as an anti-HIV agent, a pharmaceutically acceptable salt thereof, and a solvate thereof. In addition, the present invention relates to a pharmaceutical composition comprising the derivative or a pharmaceutically acceptable salt thereof, or a solvate thereof, and a pharmaceutically acceptable carrier; an anti-HIV agent, an HIV integrase inhibitor and the like, comprising the derivative or a pharmaceutically acceptable salt thereof, or a solvate thereof as an active ingredient; an anti-HIV agent comprising a combination of the derivative or a pharmaceutically acceptable salt thereof, or a solvate thereof, and one or more kinds of other anti-HIV active substances; and the like.

Background Art

[0002]

HIV (Human Immunodeficiency Virus (type 1)) belonging to retrovirus is a causative virus of AIDS (Acquired Immunodeficiency Syndrome).

HIV targets CD4 positive cell groups such as helper T cell, macrophage and dendritic cell and destroys these immunocompetent cells to cause immunodeficiency.

Accordingly, a medicament that eradicates HIV in a living organism or suppresses its growth is effective for the prophylaxis or treatment of AIDS.

[0003]

HIV possesses a bimolecular RNA gene in a shell, which is covered with an envelope protein. The RNA codes for several enzymes (protease, reverse transcriptase, integrase)

characteristic of the virus and the like. Translated reverse transcriptase and integrase are present in the shell, and protease is present inside and outside the shell.

HIV contacts and invades a host cell, causes uncoating, and releases a complex of RNA and integrase and the like into the cytoplasm. From the RNA, DNA is transcribed by reverse transcriptase, and a full length double stranded DNA is produced. The DNA moves into the nucleus of the host cell and is incorporated by integrase into the DNA of the host cell. The incorporated DNA is converted to an mRNA by polymerase of the host cell, from which mRNA various proteins necessary for forming a virus are synthesized by HIV protease and the like, and a virus particle is finally formed, which then undergoes budding and its release.

[0004]

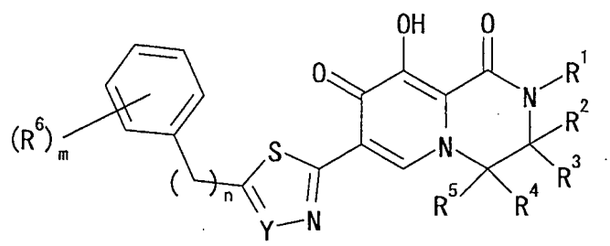
These virus specific enzymes are considered to be essential for the growth of HIV. These enzymes are drawing attention as the target of the development of antiviral agents, and several anti-HIV agents have been already developed.

For example, zidovudine, didanosine, lamivudine and the like have been already on the market as reverse transcriptase inhibitors, and indinavir, nelfinavir and the like as protease inhibitors.

In addition, a multiple drug combination therapy using these medicaments in combination (to be also referred to as HAART (highly active antiretroviral therapy)) is also used. For example, 3 agent combination therapy using two agents from reverse transcriptase inhibitors (zidovudine and lamivudine, or tenofovir and emtricitabine), and a non-nucleic acid reverse transcriptase inhibitor (efavirenz), or a protease inhibitor (lopinavir, fosamprenavir or atazanavir) in combination with ritonavir, and the like is used in clinical practice, and such multiple drug combination therapy is becoming the mainstream of the AIDS treatment.

Claims

[Claim 1] A compound represented by the following formula [I] or a pharmaceutically acceptable salt thereof, or a solvate thereof:



[I]

wherein

R^1 is

(1) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from

(i) a C_{3-8} cycloalkyl group, and

(ii) a C_{1-6} alkoxy group,

(2) a C_{3-8} cycloalkyl group, or

(3) a saturated monocyclic heterocyclic group containing, besides carbon atom, 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom,

R^2, R^3, R^4 and R^5 are the same or different and each is

(1) a hydrogen atom,

(2) a carboxyl group,

(3) $-CO-NR^aR^b$ wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the following group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by

the same or different 1 to 5 substituents selected from the following group B,

(4) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the following group A, or

(5) a cyano group,

or

R^2 and R^3, or R^4 and R^5 optionally form, together with the carbon atom bonded thereto,

i) C_{3-8} cycloalkane, or

ii) a saturated monocyclic hetero ring containing, besides carbon atom, 1 to 6 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom,

wherein R^2, R^3, R^4 and R^5 are not hydrogen atoms at the same time,

R^6 is

(1) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 halogen atoms,

(2) a C_{1-6} alkoxy group,

(3) a halogen atom, or

(4) a C_{3-8} cycloalkyl group,

Y is

(1) CH, or

(2) a nitrogen atom,

m is an integer of 1 to 5, and when m is an integer of 2 to 5, then each R^6 may be the same or different, and

n is an integer of 1 to 3,

group A:

(a) $-CO-NR^{A1}R^{A2}$

wherein R^{A1} and R^{A2} are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the following group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^{A1} and R^{A2} optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from the following group B,

(b) a hydroxyl group,

(c) a C_{1-6} alkoxy group,

(d) a C_{1-6} alkoxy-C_{1-6} alkoxy group,

(e) a cyano group,

(f) $-NR^{A3}R^{A4}$

wherein R^{A3} and R^{A4} are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group,

(iii) a C_{1-6} alkyl-carbonyl group, or

(iv) a C_{1-6} alkyl-sulfonyl group, or

R^{A3} and R^{A4} optionally form, together with the nitrogen atom bonded thereto, a hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by 1 or 2 oxo groups,

(g) a carboxyl group,

(h) a C_{1-6} alkyl-sulfonyl group, and

(i) a C_{1-6} alkyl-carbonyl group;

group B:

(a) a hydroxyl group,

(b) a C_{1-6} alkoxy group,

(c) a C_{1-6} alkoxy-C_{1-6} alkyl group

(d) a C_{3-8} cycloalkyl group, and

(e) an oxo group.

[Claim 2] The compound according to claim 1, wherein R^1 is a C_{1-6} alkyl group optionally substituted by the same or different 1

to 5 substituents selected from

(i) a C_{3-8} cycloalkyl group, and

(ii) a C_{1-6} alkoxy group,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 3] The compound according to claim 2, wherein R^1 is a C_{1-6} alkyl group, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 4] The compound according to claim 2, wherein R^1 is a C_{1-6} alkyl group substituted by a C_{3-8} cycloalkyl group, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 5] The compound according to claim 1, wherein R^1 is a C_{3-8} cycloalkyl group, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 6] The compound according to claim 1, wherein one of R^2, R^3, R^4 and R^5 is $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from group B,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 7] The compound according to claim 1, wherein one of R^2, R^3, R^4 and R^5 is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A, or a pharmaceutically acceptable salt thereof, or a solvate

thereof.

[Claim 8] The compound according to claim 1, wherein R^6 is a halogen atom, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

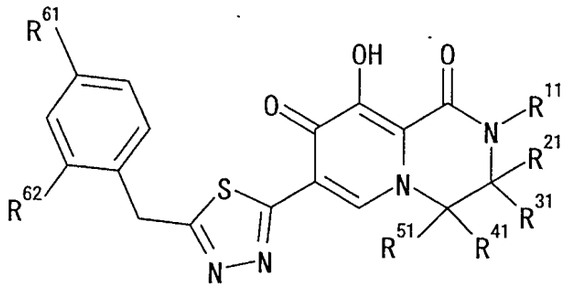
[Claim 9] The compound according to claim 1, wherein Y is CH, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 10] The compound according to claim 1, wherein Y is a nitrogen atom, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 11] The compound according to claim 1, wherein m is 1 or 2, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 12] The compound according to claim 1, wherein n is 1, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 13] The compound according to claim 1, which is represented by the following formula [I-1], or a pharmaceutically acceptable salt thereof, or a solvate thereof:



[I-1]

wherein

R^{11} is

(1) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from

(i) a C_{3-8} cycloalkyl group, and

(ii) a C_{1-6} alkoxy group, or

(2) a C_{3-8} cycloalkyl group,

R^{21}, R^{31}, R^{41} and R^{51} are the same or different and each is

(1) a hydrogen atom,

(2) $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from group B, or

(3) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A,

wherein R^{21}, R^{31}, R^{41} and R^{51} are not hydrogen atoms at the same time,

R^{61} is a halogen atom, and

R^{62} is a hydrogen atom or a halogen atom.

[Claim 14] The compound according to claim 13, wherein R^{21} is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A, and

R^{31}, R^{41} and R^{51} are each a hydrogen atom,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 15] The compound according to claim 13, wherein R^{21} is a C_{1-6} alkyl group, and

R^{31}, R^{41} and R^{51} are each a hydrogen atom,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 16] The compound according to claim 13, wherein R^{41} is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A, and

R^{21}, R^{31} and R^{51} are each a hydrogen atom,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

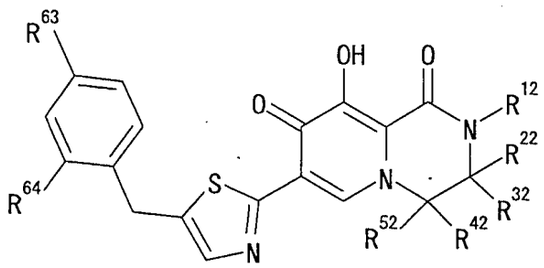
[Claim 17] The compound according to claim 13, wherein R^{21} is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A,

R^{41} is a C_{1-6} alkyl group, and

R^{31} and R^{51} are each a hydrogen atom,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 18] The compound according to claim 1, which is represented by the following formula [I-2], or a pharmaceutically acceptable salt thereof, or a solvate thereof:



[I-2]

wherein

R^{12} is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from

(i) a C_{3-8} cycloalkyl group, and

(ii) a C_{1-6} alkoxy group,

R^{22}, R^{32}, R^{42} and R^{52} are the same or different and each is

(1) a hydrogen atom,

(2) $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring

optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from group B, or

(3) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A,

wherein R^{22}, R^{32}, R^{42} and R^{52} are not hydrogen atoms at the same time,

R^{63} is a halogen atom, and

R^{64} is a hydrogen atom or a halogen atom.

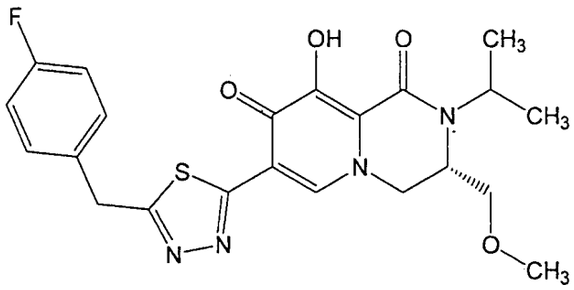
[Claim 19] The compound according to claim 18, wherein R^{42} is -CO-NR^aR^b wherein R^a and R^b form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from group B,

R^{52} is a C_{1-6} alkyl group, and

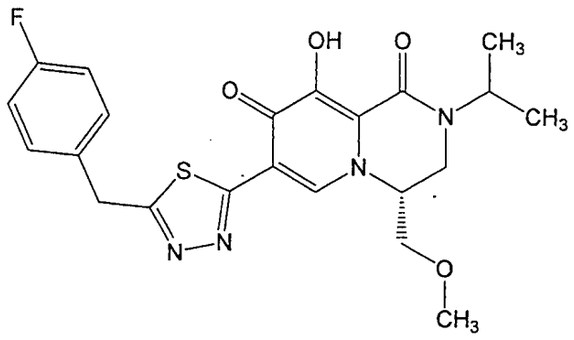
R^{22} and R^{32} is a hydrogen atom,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

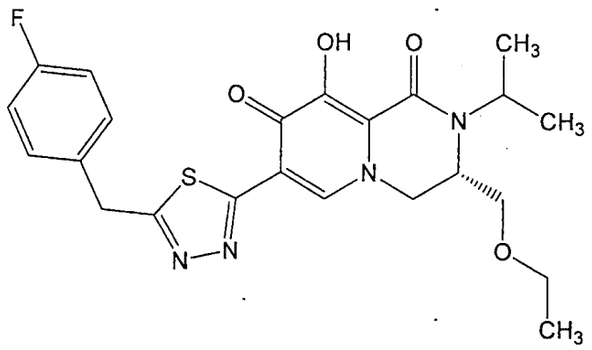
[Claim 20] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



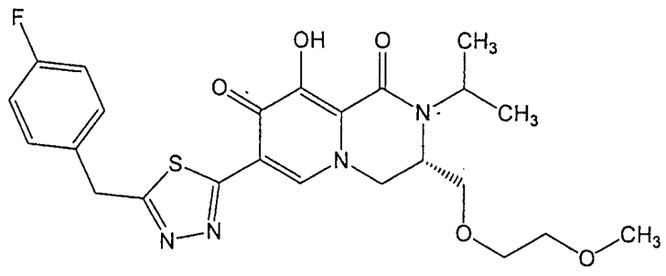
[Claim 21] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



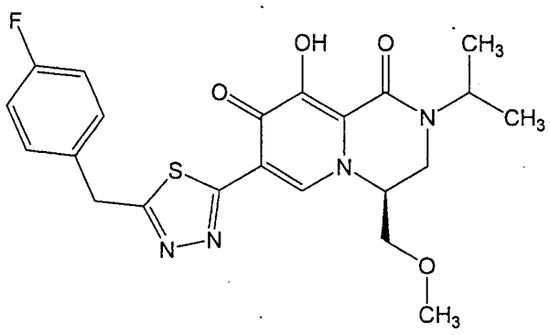
[Claim 22] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



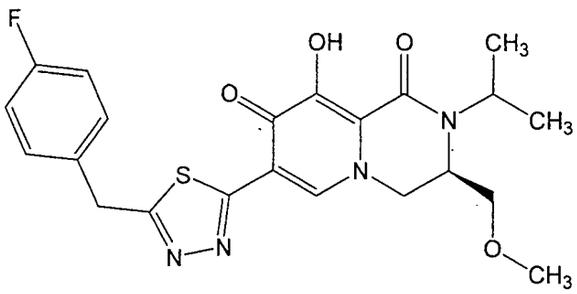
[Claim 23] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



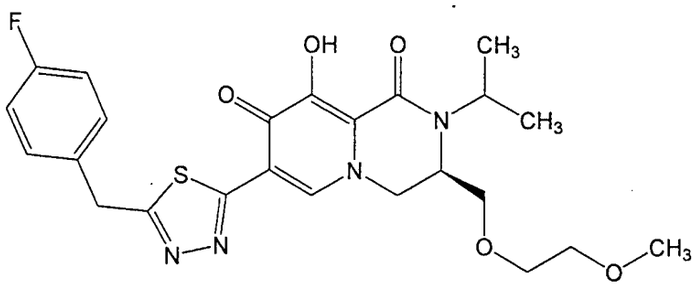
[Claim 24] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



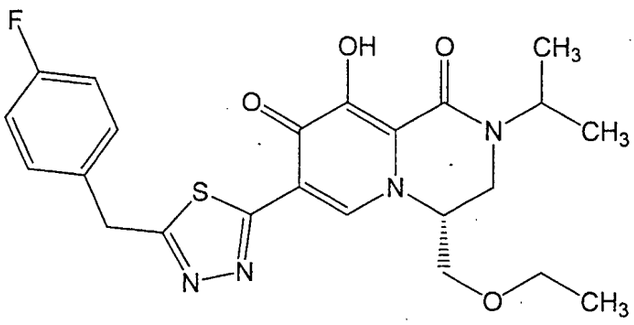
[Claim 25] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



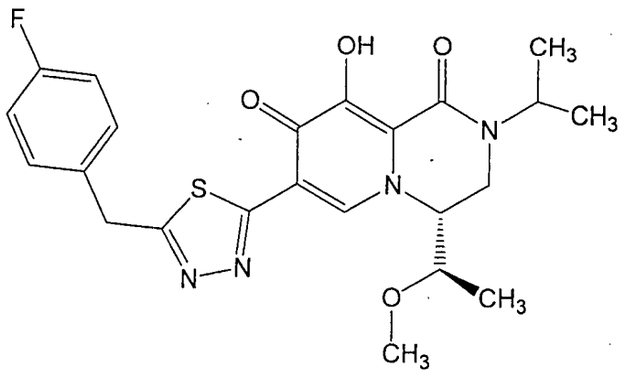
[Claim 26] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



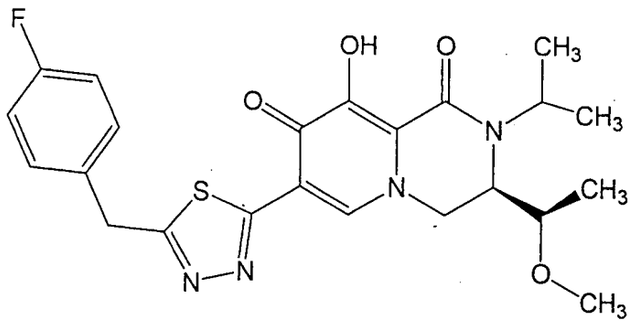
[Claim 27] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



[Claim 28] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



[Claim 29] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



[Claim 30] A pharmaceutical composition comprising the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, and a pharmaceutically acceptable carrier.

[Claim 31] An anti-HIV agent comprising the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, as an active ingredient.

[Claim 32] An HIV integrase inhibitor comprising the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, as an active ingredient.

[Claim 33] An anti-HIV agent comprising the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, in combination with one or

more other kinds of anti-HIV active substances.

[Claim 34] Use of the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, for the production of an anti-HIV agent.

[Claim 35] Use of the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, for the production of an HIV integrase inhibitor.

[Claim 36] A method for the prophylaxis or treatment of an HIV infectious disease in a mammal, which comprises administering an effective amount of the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, to said mammal.

[Claim 37] The method according to claim 36, which further comprises administering an effective amount of one or more other kinds of anti-HIV active substances to the mammal.

[Claim 38] A method for inhibiting HIV integrase in a mammal, which comprises administering an effective amount of the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, to said mammal.

[Claim 39] An anti-HIV composition comprising the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, and a pharmaceutically acceptable carrier.

[Claim 40] A pharmaceutical composition for inhibiting HIV integrase, comprising the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, and a pharmaceutically acceptable carrier.

[Claim 41] A commercial package comprising the pharmaceutical composition according to claim 30 and a written matter associated therewith, which states that the pharmaceutical composition can or should be used for treating HIV.

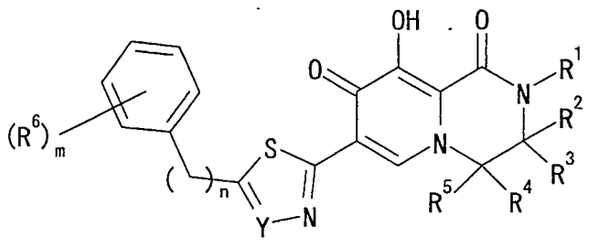
[Claim 42] A kit comprising the pharmaceutical composition

according to claim 30 and a written matter associated therewith, which states that the pharmaceutical composition can or should be used for treating HIV.

Abstract

Provided is a novel 1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrazine derivative or a pharmaceutically acceptable salt thereof, or a solvate thereof, which is useful as an anti-HIV agent.

The present invention provides a compound represented by the following formula [I]



[I]

wherein each symbol is as defined in the specification, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

SEQUENCE LISTING

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<120> 1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-a]PYRAZINE DERIVATIVE AND USE OF THE SAME AS HIV INTEGRASE INHIBITOR

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<151> 2010-02-26

<150> US 61/339729
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DERIVADO DE 1,3,4,8–TETRAHIDRO–2H–PIRIDO[1,2–a]PIRAZINA Y SU USO COMO INHIBIDOR DE LA INTEGRASA DEL VIH

CAMPO TÉCNICO DE LA INVENCIÓN

La presente invención se refiere a un nuevo derivado de 1,3,4,8–tetrahidro–2H–pirido[1,2–a]pirazina útil como un agente anti–VIH, una sal farmacéuticamente aceptable del mismo y un solvato del mismo. Además, la presente invención se refiere a una composición farmacéutica que comprende el derivado o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, y un portador farmacéuticamente aceptable; un agente anti–VIH, un inhibidor de la integrasa del VIH y similares, que comprende el derivado o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo como un ingrediente activo; un agente anti–VIH que comprende una combinación del derivado o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, y uno o más tipos de otras sustancias activas anti–VIH; y similares.

ANTECEDENTES DE LA INVENCIÓN

El VIH (virus de inmunodeficiencia humana (tipo 1)) que pertenece a los retrovirus es un virus causante del sida (síndrome de inmunodeficiencia adquirida).

El VIH se dirige a grupos de células CD4 positivas tales como célula T ayudante, macrófago y célula dendrítica y destruye estas células inmunocompetentes para provocar la inmunodeficiencia.

En consecuencia, un medicamento que erradica el VIH en un organismo vivo o suprime su crecimiento es efectivo para la profilaxis o el tratamiento de sida.

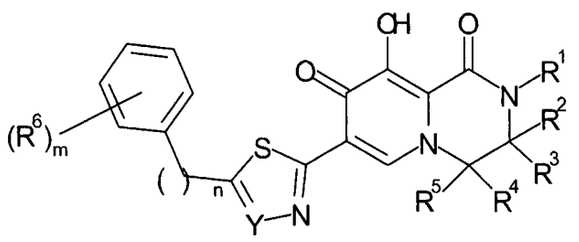
El VIH posee un gen de ARN bimolecular en una concha que se recubre con una proteína de envoltura. El ARN codifica varias enzimas (proteasa, transcriptasa inversa, integrasa) características del virus, y similares. La transcriptasa inversa traducida y la integrasa están presentes en la concha y la proteasa está presente dentro y fuera de la concha.

El VIH entra en contacto e invade una célula huésped, causa el descubrimiento y libera un complejo de ARN e integrasa, y similares en el citoplasma. Del ARN, el ADN se transcribe por transcriptasa inversa y se produce un ADN bicatenario de longitud completa. El ADN se mueve al núcleo de la célula huésped y es incorporado por la integrasa en el ADN de la célula huésped. El ADN incorporado es convertido en un ARNm por polimerasa de la célula huésped, de cuyo ARNm se sintetizan diversas

NOVEDAD DE LA INVENCIÓN

REIVINDICACIONES

1.- Un compuesto representado por la siguiente fórmula [I] o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



[I]

en donde R^1 es (1) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de (i) un grupo cicloalquilo de C_{3-8}, y (ii) un grupo alcoxi de C_{1-6}, (2) un grupo cicloalquilo de C_{3-8}, o (3) un grupo heterocíclico monocíclico saturado que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, R^2, R^3, R^4 y R^5 son iguales o diferentes y cada uno es (1) un átomo de hidrógeno, (2) un grupo carboxilo, (3) $-CO-NR^aR^b$, en donde R^a y R^b son iguales o diferentes y cada uno es (i) un átomo de hidrógeno, (ii) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B, o (iii) un grupo cicloalquilo de C_{3-8}, o R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico

saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B, (4) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo A, o (5) un grupo ciano, o R^2 y R^3, o R^4 y R^5 forman opcionalmente, junto con el átomo de carbono al que están unidos, i) cicloalcano de C_{3-8}, o ii) un heteroanillo monocíclico saturado que contiene, además de átomos de carbono, 1 a 6 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, en donde R^2, R^3, R^4 y R^5 no son átomos de hidrógeno al mismo tiempo, R^6 es (1) un grupo alquilo de C_{1-6} opcionalmente sustituido con los 1 a 5 átomos de halógeno iguales o diferentes, (2) un grupo alcoxi de C_{1-6}, (3) un átomo de halógeno, o (4) un grupo cicloalquilo de C_{3-8}, Y es (1) CH, o (2) un átomo de nitrógeno, m es un número entero de 1 a 5 y cuando m es un número entero de 2 a 5, entonces cada R^6 puede ser igual o diferente, y n es un número entero de 1 a 3, grupo A: (a) $-CO-NR^{A1}R^{A2}$, en donde R^{A1} y R^{A2} son iguales o diferentes y cada uno es (i) un átomo de hidrógeno, (ii) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B, o (iii) un grupo cicloalquilo de C_{3-8}, o R^{A1} y R^{A2} forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de

átomos de carbono y un átomo de nitrógeno, 1 a 3 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B, (b) un grupo hidroxilo, (c) un grupo alcoxi de C_{1-6}, (d) un grupo alcoxi de C_{1-6}–alcoxi de C_{1-6}, (e) un grupo ciano, (f) –$NR^{A3}R^{A4}$, en donde R^{A3} y R^{A4} son iguales o diferentes y cada uno es (i) un átomo de hidrógeno, (ii) un grupo alquilo de C_{1-6}, (iii) un grupo alquilcarbonilo de C_{1-6}, o (iv) un grupo alquilsulfonilo de C_{1-6}, o R^{A3} y R^{A4} forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 ó 2 grupos oxo, (g) un grupo carboxilo, (h) un grupo alquilsulfonilo de C_{1-6}, e (i) un grupo alquilcarbonilo de C_{1-6}; grupo B: (a) un grupo hidroxilo, (b) un grupo alcoxi de C_{1-6}, (c) un grupo alcoxi de C_{1-6}–alquilo de C_{1-6}, (d) un grupo cicloalquilo de C_{3-8}, y (e) un grupo oxo.

2.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque R^1 es un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de (i) un grupo cicloalquilo de C_{3-8}, y (ii) un grupo alcoxi de C_{1-6}, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

3.- El compuesto de conformidad con la reivindicación 2, caracterizado además porque R^1 es un grupo alquilo de C_{1-6}, o una sal

farmacéuticamente aceptable del mismo, o un solvato del mismo.

4.- El compuesto de conformidad con la reivindicación 2, caracterizado además porque R^1 es un grupo alquilo de C_{1-6} sustituido con un grupo cicloalquilo de C_{3-8}, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

5.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque R^1 es un grupo cicloalquilo de C_{3-8}, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

6.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque uno de R^2, R^3, R^4 y R^5 es $-CO-NR^aR^b$ en donde R^a y R^b son iguales o diferentes y cada uno es (i) un átomo de hidrógeno, (ii) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o (iii) un grupo cicloalquilo de C_{3-8}, o R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

7.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque uno de R^2, R^3, R^4 y R^5 es un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes

seleccionados de grupo A, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

8.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque R^6 es un átomo de halógeno, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

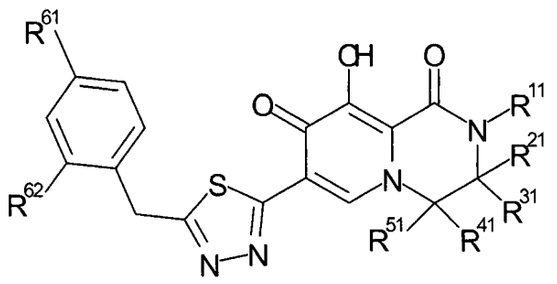
9.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque Y es CH, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

10.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque Y es un átomo de nitrógeno, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

11.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque m es 1 ó 2, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

12.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque n es 1, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

13.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la siguiente fórmula [I–1], o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



[I-1]

en donde R^{11} es (1) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de (i) un grupo cicloalquilo de C_{3-8}, y (ii) un grupo alcoxi de C_{1-6}, o (2) un grupo cicloalquilo de C_{3-8}, R^{21}, R^{31}, R^{41} y R^{51} son iguales o diferentes y cada uno es (1) un átomo de hidrógeno, (2) $-CO-NR^aR^b$ en donde R^a y R^b son iguales o diferentes y cada uno es (i) un átomo de hidrógeno, (ii) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o (iii) un grupo cicloalquilo de C_{3-8}, o R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o (3) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A, en donde R^{21}, R^{31}, R^{41} y R^{51} no son átomos de hidrógeno al mismo tiempo, R^{61} es un átomo de halógeno, y R^{62} es un átomo de hidrógeno o un átomo de halógeno.

14.- El compuesto de conformidad con la reivindicación 13, caracterizado además porque R^{21} es un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A, y R^{31}, R^{41} y R^{51} son cada uno un átomo de hidrógeno, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

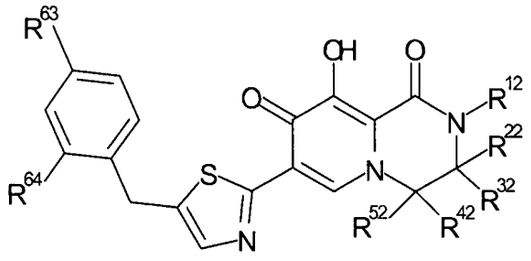
15.- El compuesto de conformidad con la reivindicación 13,

caracterizado además porque R^{21} es un grupo alquilo de C_{1-6}, y R^{31}, R^{41} y R^{51} son cada uno un átomo de hidrógeno, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

16.- El compuesto de conformidad con la reivindicación 13, caracterizado además porque R^{41} es un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A, y R^{21}, R^{31} y R^{51} son cada uno un átomo de hidrógeno, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

17.- El compuesto de conformidad con la reivindicación 13, caracterizado además porque R^{21} es un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A, R^{41} es un grupo alquilo de C_{1-6}, y R^{31} y R^{51} son cada uno un átomo de hidrógeno, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

18.- El compuesto de acuerdo con la reivindicación 1, caracterizado además porque está representado por la siguiente fórmula [I–2], o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



[I-2]

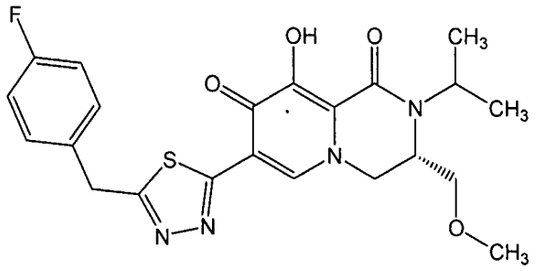
en donde R^{12} es un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de (i) un grupo cicloalquilo de

C_{3-8}, y (ii) un grupo alcoxi de C_{1-6}, R^{22}, R^{32}, R^{42} y R^{52} son iguales o diferentes y cada uno es (1) un átomo de hidrógeno, (2) $-CO-NR^aR^b$ en donde R^a y R^b son iguales o diferentes y cada uno es (i) un átomo de hidrógeno, (ii) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o (iii) un grupo cicloalquilo de C_{3-8}, o R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o (3) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A, en donde R^{22}, R^{32}, R^{42} y R^{52} no son átomos de hidrógeno al mismo tiempo, R^{63} es un átomo de halógeno, y R^{64} es un átomo de hidrógeno o un átomo de halógeno.

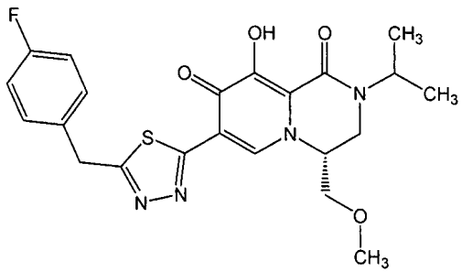
19.- El compuesto de conformidad con la reivindicación 18, caracterizado además porque R^{42} es $-CO-NR^aR^b$, en donde R^a y R^b forman, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, R^{52} es un grupo alquilo de C_{1-6}, y R^{22} y R^{32} es un

átomo de hidrógeno, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

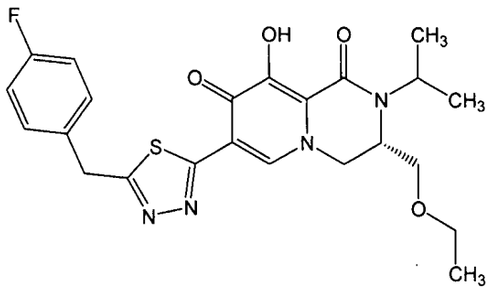
20.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



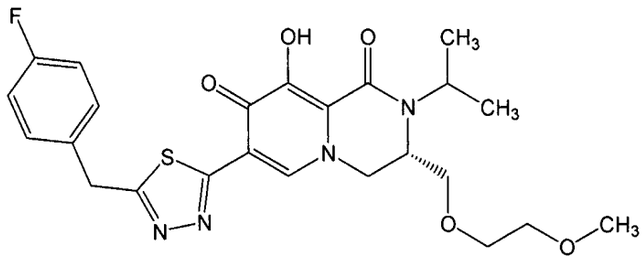
21.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



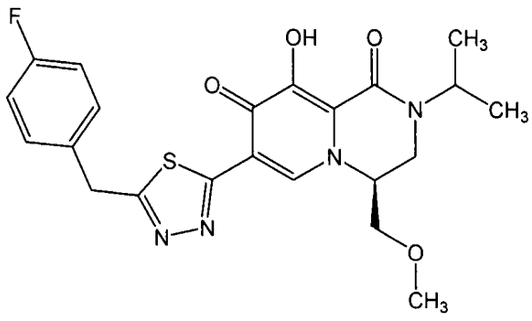
22.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



23.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:

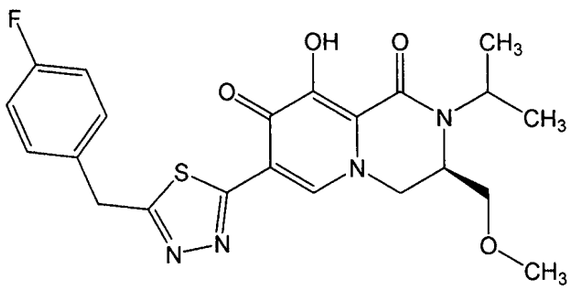


24.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:

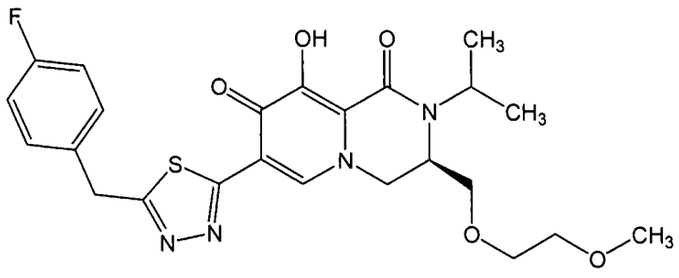


25.- El compuesto de conformidad con la reivindicación 1,

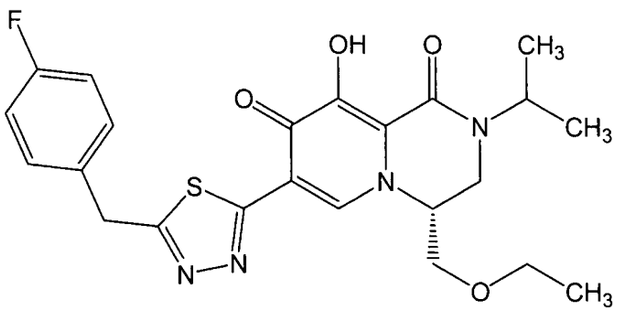
caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



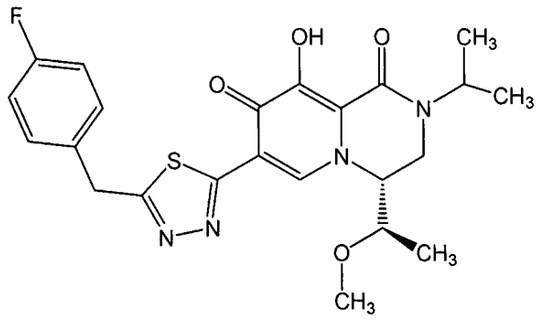
26.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



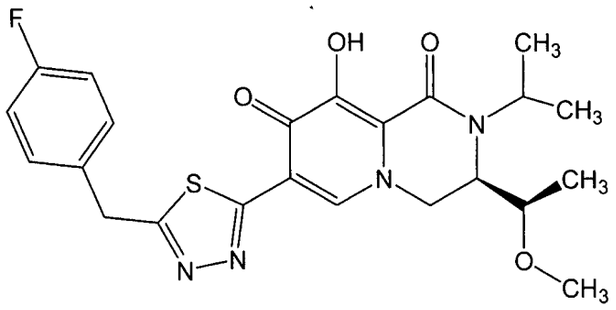
27.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



28.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



29.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



30.- Una composición farmacéutica que comprende el compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, y un portador farmacéuticamente aceptable.

31.- Un agente anti–VIH que comprende el compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, como un ingrediente activo.

32.- Un inhibidor de la integrasa del VIH que comprende el compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, como un ingrediente activo.

33.- Un agente anti–VIH que comprende el compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, en combinación con uno o más de otros tipos de sustancias activas anti–VIH.

34.- El uso del compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, para la producción de un agente anti–VIH.

35.- El uso del compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, para la producción de un inhibidor de la integrasa del VIH.

36.- Un método para la profilaxis o el tratamiento de una enfermedad infecciosa de VIH en un mamífero, el cual comprende la administración de una cantidad efectiva del compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, a dicho mamífero.

37.- El método de conformidad con la reivindicación 37, caracterizado además porque comprende adicionalmente la administración de una cantidad efectiva de uno o más de otros tipos de sustancias activas anti–VIH al mamífero.

38.- Un método para inhibir la integrasa del VIH en un mamífero, el cual comprende la administración de una cantidad efectiva del compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, a dicho mamífero.

39.- Una composición anti–VIH que comprende el compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, y un portador farmacéuticamente aceptable.

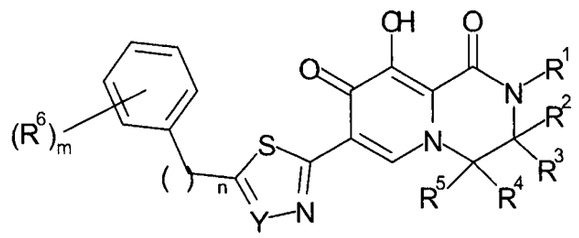
40.- Una composición farmacéutica para inhibir la integrasa del VIH, que comprende el compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, y un portador farmacéuticamente aceptable.

41.- Un envase comercial que comprende la composición farmacéutica de la reivindicación 30 y un material escrito asociado con la misma, que establece que la composición farmacéutica se puede o se debe usar para tratar el VIH.

42.- Un kit que comprende la composición farmacéutica de la reivindicación 30 y un material escrito asociado con la misma, que establece que la composición farmacéutica se puede o se debe usar para tratar el VIH.

RESUMEN DE LA INVENCIÓN

Se provee un nuevo derivado de 1,3,4,8–tetrahidro–2H–pirido[1,2–a]pirazina o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, que es útil como un agente anti–VIH; la presente invención provee un compuesto representado por la siguiente fórmula [I]



[I]

en donde cada símbolo es como se define en la especificación, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

LISTADO DE SECUENCIAS

<110> Solicitante: Japan Tobacco Inc.

<120> Título de la invención: 1,3,4,8-TETRAHIDRO-2H-PIRIDO[1,2-a]PIRAZINA Y SU USO COMO INHIBIDOR DE LA INTEGRASA DEL VIH

<130> Referencia de expediente: 091655

<150> Número de solicitud anterior: JP 2010-043567
<151> Fecha de presentación de solicitud anterior: 26-02-2010

<150> Número de solicitud anterior: US 61/339729
<151> Fecha de presentación de solicitud anterior: 09-03-2010

<160> Número de SEQ ID NOs: 4

<170> Software: PatentIn versión 3.5

<210> SEQ ID NO.: 1
<211> Longitud: 32
<212> Tipo: ADN
<213> Organismo: Secuencia artificial

<220> Característica:
<223> Otra información: Cadena más donante para la determinación de la actividad de la VIH integrasa

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<213> Organismo: Secuencia artificial

<220> Característica:
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Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia:	Fecha: ____/____/____ AAAA MM DD	Recorrido:
Tipo de Radicación: Entrada: ☐ Salida: ☐ Traslado: ☐ Convenio: ☐		
Radicador:		Planilla:

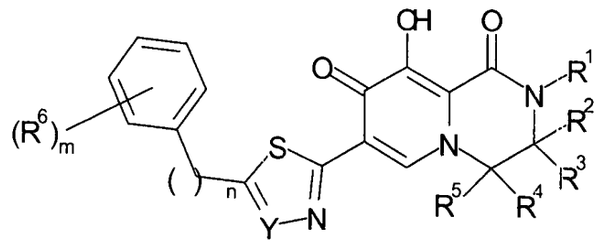
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Item	*Unidad de Conservación*
1	Bolsa
2	Caja
3	Libro
4	Sobre
5	Tomo
6	Otro
Item	*Soporte Documental*
7	CD
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
10	Otro

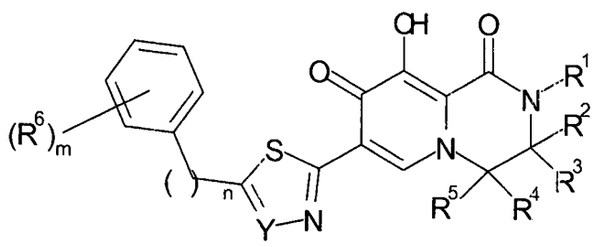
Observaciones:

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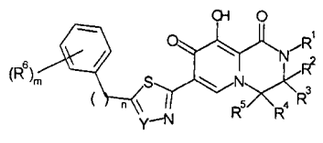
CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA



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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ____ PCT __X__ MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

(21) Nº de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s) **JAPAN TOBACCO INC.**

(72) Inventor(es) **MIYAZAKI, Susumu; BESSHO, Yuki; ADACHI, Kaoru; KAWASHITA, Seiji; ISOSHIMA, Hirotaka; OSHITA, Kengo; FUKUDA, Shunichi**

(74) Apoderado: **DRA. MARGARITA CASTELLANOS ABONDANO**

(30) Prioridad	(31)	**No. Prioridad**	32)	**Fecha**	(33)	**País**
		043567/2010		**2010/02/26**		**JP**
		61/339.729		**2010/03/09**		**US**

(85) Fecha inicio fase nacional:
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: **2011/02/25**
No. de solicitud **PCT/JP2011/054404**

(87) Publicación internacional
Fecha: **2011/09/01**
Nº publicación: **WO 2011/105590 A1**

(54) Titulo: **DERIVADO DE 1,3,4,8–TETRAHIDRO–2H–PIRIDO[1,2–a]PIRAZINA Y SU USO COMO INHIBIDOR DE LA INTEGRASA DEL VIH**

Industria y Comercio
SUPERINTENDENCIA

EXTRACTO PARA PUBLICACIÓN

___ Patente de Invención ___ Patente modelo de utilidad _X_ PCT

(21) No. De solicitud	(51) int. Cl:
(22) Fecha de solicitud	(71) Solicitante (s) **JAPAN TOBACCO INC.**
(30) Prioridad (31) No. Prioridad **043567/2010, 61/339.729** (32) Fecha **2010/02/26, 2010/03/09** (33) País **JP, US**	(72) Interventor (es) **MIYAZAKI, Susumu** **BESSHO, Yuki** **ADACHI, Kaoru** **KAWASHITA, Seiji** **ISOSHIMA, Hirotaka** **OSHITA, Kengo** **FUKUDA, Shunichi** (74) Apoderado (s) **DRA. MARGARITA CASTELLANOS ABONDANO**

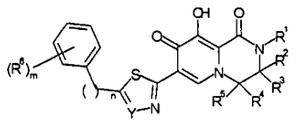
(54) Título
DERIVADO DE 1,3,4,8–TETRAHIDRO–2H–PIRIDO[1,2–a]PIRAZINA Y SU USO COMO INHIBIDOR DE LA INTEGRASA DEL VIH

Las casillas identificadas con 85, 86 y 87 sólo aplican para PCT

(85) Fecha límite inicio Fase Nacional	
(86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud **2011/02/25** No. de solicitud **PCT/JP2011/054404**	(87) Publicación internacional Fecha **2011/09/01** No. Publicación **WO 2011/105590 A1**

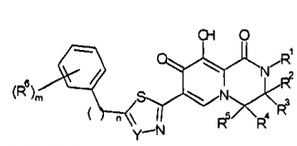
Resumen reivindicación (es):

1. Un compuesto representado por la siguiente fórmula [I] o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



[I]

en donde R^1 es (1) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de (i) un grupo cicloalquilo de C_{3-8}, y (ii) un grupo alcoxi de C_{1-6}, (2) un grupo cicloalquilo de C_{3-8}, o (3) un grupo heterocíclico monocíclico saturado que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, R^2, R^3, R^4 y R^5 son iguales o diferentes y cada uno es (1) un átomo de hidrógeno, (2) un grupo carboxilo, (3) –CO–NR^aR^b, en donde R^a y R^b son iguales o diferentes y cada uno es (i) un átomo de hidrógeno, (ii) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B, o (iii) un grupo cicloalquilo de C_{3-8}, o R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B, (4) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo A, o (5) un grupo ciano, o R^2 y R^3, o R^4 y R^5 forman opcionalmente, junto con el átomo de carbono al que están unidos, i) cicloalcano de C_{3-8}, o ii) un heteroanillo monocíclico saturado que contiene, además de átomos de carbono, 1 a 6 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, en donde R^2, R^3, R^4 y R^5 no son átomos de hidrógeno al mismo tiempo, R^6 es (1) un grupo alquilo de C_{1-6} opcionalmente sustituido con los 1 a 5 átomos de halógeno iguales o diferentes, (2) un grupo alcoxi de C_{1-6}, (3) un átomo de halógeno, o (4) un grupo cicloalquilo de C_{3-8}, Y es (1) CH, o (2) un átomo de nitrógeno, m es un número entero de 1 a 5 y cuando m es un número entero de 2 a 5, entonces cada R^6 puede ser igual o diferente, y n es un número entero de 1 a 3, grupo A: (a) –CO–$NR^{A1}R^{A2}$, en donde R^{A1} y R^{A2} son iguales o diferentes y cada uno es (i) un átomo de hidrógeno, (ii) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B, o (iii) un grupo cicloalquilo de C_{3-8}, o R^{A1} y R^{A2} forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 3 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B, (b) un grupo hidroxilo, (c) un grupo alcoxi de C_{1-6}, (d) un grupo alcoxi de C_{1-6}–alcoxi de C_{1-6}, (e) un grupo ciano, (f) –$NR^{A3}R^{A4}$, en donde R^{A3} y R^{A4} ...



[I]

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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PATENTE DE INVENCIÓN _____ **MODELO DE UTILIDAD** _____ **Art 33 Decisión 486/00**

Indicación que se solicita una patente.
Datos de identificación del solicitante o de la persona que presenta la solicitud
Descripción de la invención
Dibujos de ser estos pertinentes
Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa _____ Incompleta _____

PATENTE DE INVENCIÓN PCT X **MODELO DE UTILIDAD PCT** ___ **Art.33 Decisión 486/00, Circular Única**

X Indicación que se solicita una PCT
X Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
Dibujos de ser estos pertinentes
X Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa X Incompleta _____

DISEÑO INDUSTRIAL _____ **(Art. 119 Decisión 486/00)**

Indicación que se solicita Diseño industrial
Datos de identificación del solicitante o de la persona que presenta la solicitud
Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño

Comprobante de pago de las tasas establecidas

Completa _____ Incompleta _____

ESQUEMA DE TRAZADO _____ **(Art. 92 Decisión 486/00)**

Indicación que se solicita un esquema de trazado

Datos de identificación del solicitante o de la persona que presenta la solicitud

Representación gráfica de un esquema de trazado

Comprobante de pago de las tasas establecidas

Completa _____ Incompleta _____

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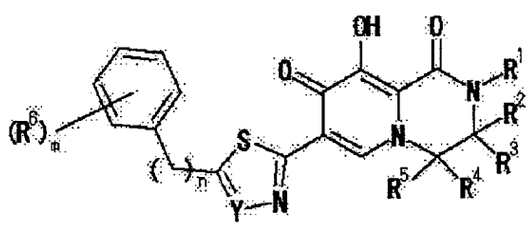
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[続葉有]

(54) Title: 1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZINE DERIVATIVE AND USE OF SAME AS HIV INTEGRASE INHIBITOR

(54) 発明の名称: １，３，４，８－テトラヒドロ－２Ｈ－ピリド［１，２－ａ］ピラジン誘導体及びそのＨＩＶインテグラーゼ阻害剤としての利用



[I]

(57) Abstract: Disclosed is a novel 1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrazine derivative, a pharmaceutically acceptable salt thereof or a solvate thereof, which is useful as an anti-HIV agent. Specifically disclosed is a compound represented by general formula (I), a pharmaceutically acceptable salt thereof or a solvate thereof. (In the formula, the symbols are as defined in the description.)

(57) 要約: 抗ＨＩＶ剤として有用な、新規１，３，４，８－テトラヒドロ－２Ｈ－ピリド［１，２－ａ］ピラジン誘導体又はその医薬上許容される塩、或いはその溶媒和物を提供する。 下記一般式［Ｉ］で表される化合物又はその医薬上許容される塩、或いはその溶媒和物に関する［式中、各記号は明細書中と同義である］。

WO 2011/105590 A1

(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

添付公開書類:

— 国際調査報告（条約第 21 条(3)）

— 明細書の別個の部分として表した配列リスト（規則 5.2(a)）

DESCRIPTION

Title of the Invention: 1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZINE DERIVATIVE AND USE OF SAME AS HIV INTEGRASE INHIBITOR

TECHNICAL FIELD

[0001]

The present invention relates to a novel 1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrazine derivative useful as an anti-HIV agent, a pharmaceutically acceptable salt thereof, and a solvate thereof. In addition, the present invention relates to a pharmaceutical composition comprising the derivative or a pharmaceutically acceptable salt thereof, or a solvate thereof, and a pharmaceutically acceptable carrier; an anti-HIV agent, an HIV integrase inhibitor and the like, comprising the derivative or a pharmaceutically acceptable salt thereof, or a solvate thereof as an active ingredient; an anti-HIV agent comprising a combination of the derivative or a pharmaceutically acceptable salt thereof, or a solvate thereof, and one or more kinds of other anti-HIV active substances; and the like.

Background Art

[0002]

HIV (Human Immunodeficiency Virus (type 1)) belonging to retrovirus is a causative virus of AIDS (Acquired Immunodeficiency Syndrome).

HIV targets CD4 positive cell groups such as helper T cell, macrophage and dendritic cell and destroys these immunocompetent cells to cause immunodeficiency.

Accordingly, a medicament that eradicates HIV in a living organism or suppresses its growth is effective for the prophylaxis or treatment of AIDS.

[0003]

HIV possesses a bimolecular RNA gene in a shell, which is covered with an envelope protein. The RNA codes for several enzymes (protease, reverse transcriptase, integrase)

characteristic of the virus and the like. Translated reverse transcriptase and integrase are present in the shell, and protease is present inside and outside the shell.

HIV contacts and invades a host cell, causes uncoating, and releases a complex of RNA and integrase and the like into the cytoplasm. From the RNA, DNA is transcribed by reverse transcriptase, and a full length double stranded DNA is produced. The DNA moves into the nucleus of the host cell and is incorporated by integrase into the DNA of the host cell. The incorporated DNA is converted to an mRNA by polymerase of the host cell, from which mRNA various proteins necessary for forming a virus are synthesized by HIV protease and the like, and a virus particle is finally formed, which then undergoes budding and its release.

[0004]

These virus specific enzymes are considered to be essential for the growth of HIV. These enzymes are drawing attention as the target of the development of antiviral agents, and several anti-HIV agents have been already developed.

For example, zidovudine, didanosine, lamivudine and the like have been already on the market as reverse transcriptase inhibitors, and indinavir, nelfinavir and the like as protease inhibitors.

In addition, a multiple drug combination therapy using these medicaments in combination (to be also referred to as HAART (highly active antiretroviral therapy)) is also used. For example, 3 agent combination therapy using two agents from reverse transcriptase inhibitors (zidovudine and lamivudine, or tenofovir and emtricitabine), and a non-nucleic acid reverse transcriptase inhibitor (efavirenz), or a protease inhibitor (lopinavir, fosamprenavir or atazanavir) in combination with ritonavir, and the like is used in clinical practice, and such multiple drug combination therapy is becoming the mainstream of the AIDS treatment.

However, some of these medicaments are known to cause side effects such as liver function failure, central nervous disorders (e.g., vertigo), and the like. In addition, acquisition of resistance to a medicament causes a problem. Even worse, emergence of an HIV that shows multiple drug resistance in a multiple drug combination therapy has been known.

[0005]

Under the circumstances, a further development of a novel medicament, particularly a development of an anti-HIV agent based on a new mechanism, has been desired, wherein a development of an anti-HIV agent having an integrase inhibitory activity is expected, because an integrase characteristic of retrovirus is an essential enzyme for the growth of HIV.

SUMMARY OF THE INVENTION

Problems to be Solved by the Invention

[0006]

From the findings obtained from pharmacological studies and clinical results heretofore, an anti-HIV agent is effective for the prophylaxis or treatment of AIDS, and particularly a compound having an integrase inhibitory activity can be an effective anti-HIV agent.

Therefore, the present invention aims at provision of a compound having an anti-HIV activity, particularly a compound having an integrase inhibitory activity.

Means of Solving the Problems

[0007]

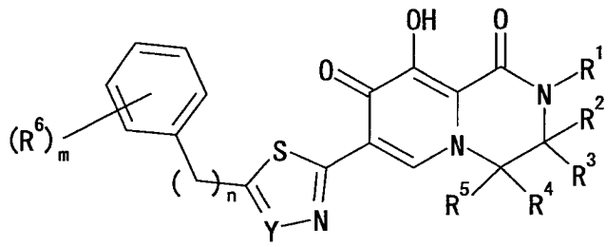
The present inventors have conducted intensive studies in an attempt to find a compound having an anti-HIV action, particularly a compound having an integrase inhibitory action, and completed the present invention.

More specifically, the present invention provides the following.

[1] A compound represented by the following formula [I] or a

pharmaceutically acceptable salt thereof, or a solvate thereof (sometimes to be abbreviated as "the compound of the present invention" in the present specification):

[0008]



[I]

[0009]

wherein

R^1 is

(1) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from

(i) a C_{3-8} cycloalkyl group, and

(ii) a C_{1-6} alkoxy group,

(2) a C_{3-8} cycloalkyl group, or

(3) a saturated monocyclic heterocyclic group containing, besides carbon atom, 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom,

R^2, R^3, R^4 and R^5 are the same or different and each is

(1) a hydrogen atom,

(2) a carboxyl group,

(3) $-CO-NR^aR^b$ wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the following group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by

the same or different 1 to 5 substituents selected from the following group B,

(4) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the following group A, or

(5) a cyano group,

or

R^2 and R^3, or R^4 and R^5 optionally form, together with the carbon atom bonded thereto,

i) C_{3-8} cycloalkane, or

ii) a saturated monocyclic hetero ring containing, besides carbon atom, 1 to 6 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom,

wherein R^2, R^3, R^4 and R^5 are not hydrogen atoms at the same time,

R^6 is

(1) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 halogen atoms,

(2) a C_{1-6} alkoxy group,

(3) a halogen atom, or

(4) a C_{3-8} cycloalkyl group,

Y is

(1) CH, or

(2) a nitrogen atom,

m is an integer of 1 to 5, and when m is an integer of 2 to 5, then each R^6 may be the same or different, and

n is an integer of 1 to 3,

group A:

(a) $-CO-NR^{A1}R^{A2}$

wherein R^{A1} and R^{A2} are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the following group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^{A1} and R^{A2} optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from the following group B,

(b) a hydroxyl group,

(c) a C_{1-6} alkoxy group,

(d) a C_{1-6} alkoxy-C_{1-6} alkoxy group,

(e) a cyano group,

(f) $-NR^{A3}R^{A4}$

wherein R^{A3} and R^{A4} are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group,

(iii) a C_{1-6} alkyl-carbonyl group, or

(iv) a C_{1-6} alkyl-sulfonyl group, or

R^{A3} and R^{A4} optionally form, together with the nitrogen atom bonded thereto, a hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by 1 or 2 oxo groups,

(g) a carboxyl group,

(h) a C_{1-6} alkyl-sulfonyl group, and

(i) a C_{1-6} alkyl-carbonyl group;

group B:

(a) a hydroxyl group,

(b) a C_{1-6} alkoxy group,

(c) a C_{1-6} alkoxy-C_{1-6} alkyl group

(d) a C_{3-8} cycloalkyl group, and

(e) an oxo group.

[2] The compound of the above-mentioned [1], wherein R^1 is a C_{1-6} alkyl group optionally substituted by the same or different 1

to 5 substituents selected from

(i) a C_{3-8} cycloalkyl group, and

(ii) a C_{1-6} alkoxy group,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[3] The compound of the above-mentioned [2], wherein R^1 is a C_{1-6} alkyl group, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[4] The compound of the above-mentioned [2], wherein R^1 is a C_{1-6} alkyl group substituted by a C_{3-8} cycloalkyl group, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[5] The compound of the above-mentioned [1], wherein R^1 is a C_{3-8} cycloalkyl group, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[6] The compound of the above-mentioned [1], wherein one of R^2, R^3, R^4 and R^5 is $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from group B,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[7] The compound of the above-mentioned [1], wherein one of R^2, R^3, R^4 and R^5 is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A, or a pharmaceutically acceptable salt thereof, or a solvate

thereof.

[8] The compound of the above-mentioned [1], wherein R^6 is a halogen atom, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[9] The compound of the above-mentioned [1], wherein Y is CH, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

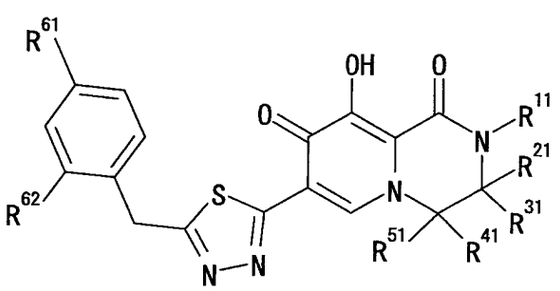
[10] The compound of the above-mentioned [1], wherein Y is a nitrogen atom, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[11] The compound of the above-mentioned [1], wherein m is 1 or 2, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[12] The compound of the above-mentioned [1], wherein n is 1, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[13] The compound of the above-mentioned [1], which is represented by the following formula [I-1], or a pharmaceutically acceptable salt thereof, or a solvate thereof:

[0010]



[I-1]

[0011]

wherein

R^{11} is

(1) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from

(i) a C_{3-8} cycloalkyl group, and

(ii) a C_{1-6} alkoxy group, or

(2) a C_{3-8} cycloalkyl group,

R^{21}, R^{31}, R^{41} and R^{51} are the same or different and each is

(1) a hydrogen atom,

(2) $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from group B, or

(3) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A,

wherein R^{21}, R^{31}, R^{41} and R^{51} are not hydrogen atoms at the same time,

R^{61} is a halogen atom, and

R^{62} is a hydrogen atom or a halogen atom.

[14] The compound of the above-mentioned [13], wherein R^{21} is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A, and

R^{31}, R^{41} and R^{51} are each a hydrogen atom,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[15] The compound of the above-mentioned [13], wherein R^{21} is a C_{1-6} alkyl group, and

R^{31}, R^{41} and R^{51} are each a hydrogen atom,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[16] The compound of the above-mentioned [13], wherein R^{41} is a C_{1-6} alkyl group optionally substituted by the same or different

1 to 5 substituents selected from group A, and

R^{21}, R^{31} and R^{51} are each a hydrogen atom,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[17] The compound of the above-mentioned [13], wherein R^{21} is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A,

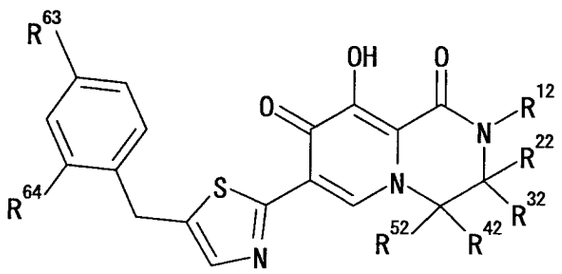
R^{41} is a C_{1-6} alkyl group, and

R^{31} and R^{51} are each a hydrogen atom,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[18] The compound of the above-mentioned [1], which is represented by the following formula [I-2], or a pharmaceutically acceptable salt thereof, or a solvate thereof:

[0012]



[I-2]

[0013]

wherein

R^{12} is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from

(i) a C_{3-8} cycloalkyl group, and

(ii) a C_{1-6} alkoxy group,

R^{22}, R^{32}, R^{42} and R^{52} are the same or different and each is

(1) a hydrogen atom,

(2) $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group B,

or

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from group B, or

(3) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A,

wherein R^{22}, R^{32}, R^{42} and R^{52} are not hydrogen atoms at the same time,

R^{63} is a halogen atom, and

R^{64} is a hydrogen atom or a halogen atom.

[19] The compound of the above-mentioned [18], wherein R^{42} is -$CO-NR^aR^b$

wherein R^a and R^b form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from group B,

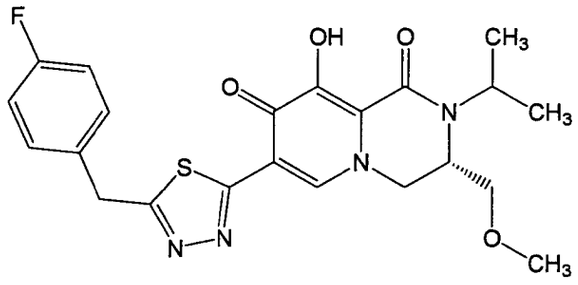
R^{52} is a C_{1-6} alkyl group, and

R^{22} and R^{32} is a hydrogen atom,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[20] The compound of the above-mentioned [1], which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:

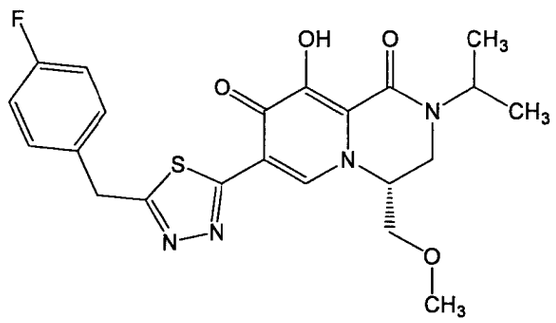
[0014]



[0015]

[21] The compound of the above-mentioned [1], which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:

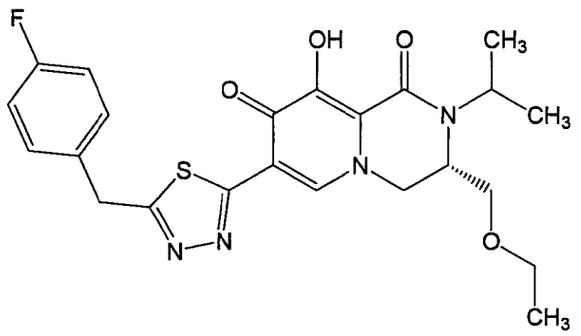
[0016]



[0017]

[22] The compound of the above-mentioned [1], which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:

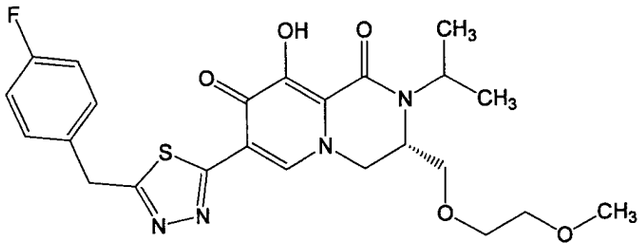
[0018]



[0019]

[23] The compound of the above-mentioned [1], which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:

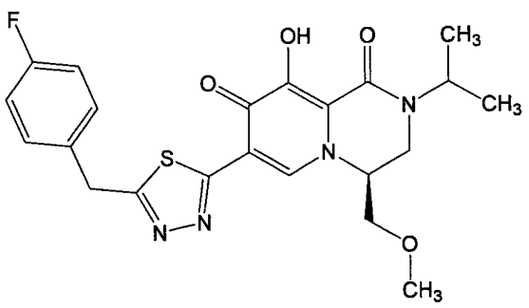
[0020]



[0021]

[24] The compound of the above-mentioned [1], which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:

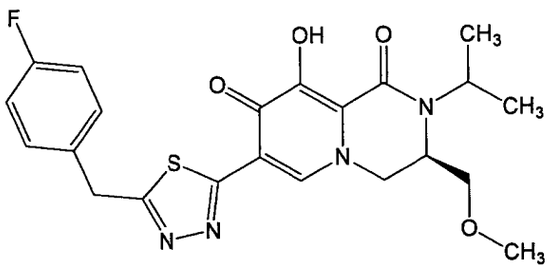
[0022]



[0023]

[25] The compound of the above-mentioned [1], which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:

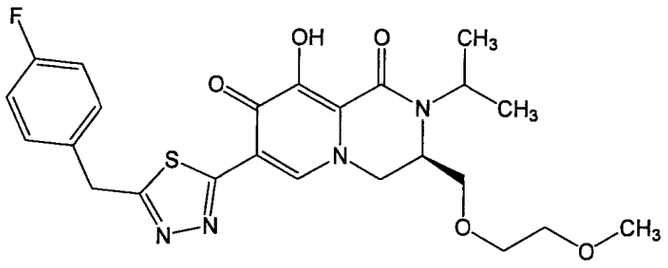
[0024]



[0025]

[26] The compound of the above-mentioned [1], which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:

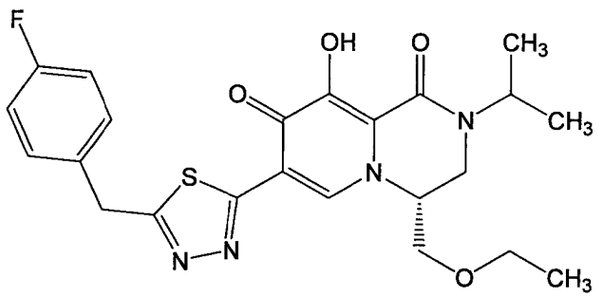
[0026]



[0027]

[27] The compound of the above-mentioned [1], which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:

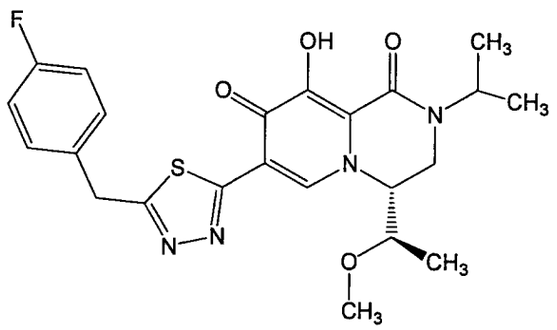
[0028]



[0029]

[28] The compound of the above-mentioned [1], which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:

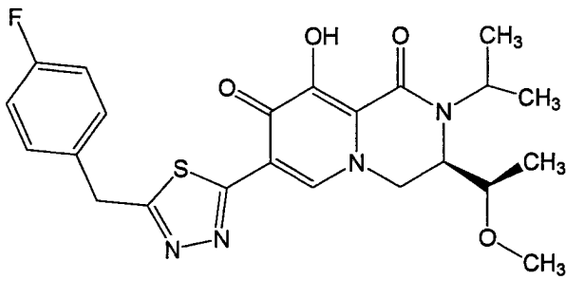
[0030]



[0031]

[29] The compound of the above-mentioned [1], which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:

[0032]



[0033]

[30] A pharmaceutical composition comprising the compound of any one of the above-mentioned [1] to [29] or a pharmaceutically acceptable salt thereof, or a solvate thereof, and a pharmaceutically acceptable carrier.

[31] An anti-HIV agent comprising the compound of any one of the above-mentioned [1] to [29] or a pharmaceutically acceptable salt thereof, or a solvate thereof, as an active ingredient.

[32] An HIV integrase inhibitor comprising the compound of any one of the above-mentioned [1] to [29] or a pharmaceutically acceptable salt thereof, or a solvate thereof, as an active ingredient.

[33] An anti-HIV agent comprising the compound of any one of the above-mentioned [1] to [29] or a pharmaceutically acceptable salt thereof, or a solvate thereof, in combination with one or more other kinds of anti-HIV active substances.

[34] Use of the compound of any one of the above-mentioned [1] to [29] or a pharmaceutically acceptable salt thereof, or a solvate thereof, for the production of an anti-HIV agent.

[35] Use of the compound of any one of the above-mentioned [1] to [29] or a pharmaceutically acceptable salt thereof, or a solvate thereof, for the production of an HIV integrase inhibitor.

[36] A method for the prophylaxis or treatment of an HIV infectious disease in a mammal, which comprises administering an effective amount of the compound of any one of the above-mentioned [1] to [29] or a pharmaceutically acceptable salt thereof, or a solvate thereof, to said mammal.

[37] The method of the above-mentioned [36], which further comprises administering an effective amount of one or more other kinds of anti-HIV active substances to the mammal.

[38] A method for inhibiting HIV integrase in a mammal, which comprises administering an effective amount of the compound of any one of the above-mentioned [1] to [29] or a pharmaceutically acceptable salt thereof, or a solvate thereof, to said mammal.

[39] An anti-HIV composition comprising the compound of any one of the above-mentioned [1] to [29] or a pharmaceutically acceptable salt thereof, or a solvate thereof, and a pharmaceutically acceptable carrier.

[40] A pharmaceutical composition for inhibiting HIV integrase, comprising the compound of any one of the above-mentioned [1] to [29] or a pharmaceutically acceptable salt thereof, or a solvate thereof, and a pharmaceutically acceptable carrier.

[41] A commercial package comprising the pharmaceutical composition of the above-mentioned [30] and a written matter associated therewith, which states that the pharmaceutical composition can or should be used for treating HIV.

[42] A kit comprising the pharmaceutical composition of the above-mentioned [30] and a written matter associated therewith, which states that the pharmaceutical composition can or should be used for treating HIV.

Effect of the Invention

[0034]

The compound of the present invention can be medicaments effective for the prophylaxis or treatment of HIV infections or AIDS, as anti-HIV agents, having an HIV integrase inhibitory activity. In addition, by a combined use with other anti-HIV agent(s) such as protease inhibitor, reverse transcriptase inhibitor and the like, they can be more effective anti-HIV agents. Furthermore, having high inhibitory activity specific for integrase, they can be medicaments safe for human body with a fewer side effects.

Description of Embodiments

[0035]

The definitions of respective substituents and respective moieties used in the present specification are as follows.

[0036]

The "halogen atom" is a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

[0037]

The "C_{1-6} alkyl group" is a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, preferably a straight chain or branched chain alkyl group having 1 to 4 carbon atoms. Specific examples include a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a pentyl group, an isopentyl group, a 1,1-dimethylpropyl group, a 1,2-dimethylpropyl group, a 2,2-dimethylpropyl group, a 1-ethylpropyl group, a hexyl group and the like.

[0038]

The "C_{1-6} alkoxy group" is a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, preferably a straight chain or branched chain alkoxy group having 1 to 4 carbon atoms. Specific examples include a methoxy group, an ethoxy group, a propoxy group, an isopropyloxy group, a butoxy group, an isobutyloxy group, a tert-butyloxy group, a pentyloxy group, a hexyloxy group and the like.

[0039]

The "C_{1-6} alkoxy-C_{1-6} alkyl group" is that wherein the alkoxy moiety is the "C_{1-6} alkoxy group" defined above, and the alkyl moiety is the "C_{1-6} alkyl group" defined above. Preferred is a C_{1-6} alkoxy-C_{1-6} alkyl group wherein the alkoxy moiety is a straight chain or branched chain alkoxy group having 1 to 4 carbon atoms, and the alkyl moiety is a straight chain or branched chain alkyl group having 1 to 4 carbon atoms. Examples of the C_{1-6} alkoxy-C_{1-6} alkyl group include a methoxymethyl group, a methoxyethyl group, a methoxypropyl

group, a methoxybutyl group, a methoxypentyl group, a methoxyhexyl group, an ethoxymethyl group, an ethoxyethyl group, an ethoxypropyl group, an ethoxybutyl group, an ethoxypentyl group, an ethoxyhexyl group, a propoxymethyl group, a propoxyethyl group, a propoxypropyl group, a propoxybutyl group, a propoxypentyl group, a propoxyhexyl group, a butoxymethyl group, a butoxyethyl group, a butoxypropyl group, a butoxybutyl group, a butoxypentyl group, a butoxyhexyl group, a pentyloxymethyl group, a pentyloxyethyl group, a pentyloxypropyl group, a pentyloxybutyl group, a pentyloxypentyl group, a pentyloxyhexyl group, a hexyloxymethyl group, a hexyloxyethyl group, a hexyloxypropyl group, a hexyloxybutyl group, a hexyloxypentyl group, a hexyloxyhexyl group and the like.

[0040]

The "C_{1-6} alkoxy-C_{1-6} alkoxy group" is that wherein the C_{1-6} alkoxy moiety is the "C_{1-6} alkoxy group" defined above, preferably a straight chain or branched chain alkoxy group having 1 to 4 carbon atoms. Examples thereof include a methoxymethoxy group, a methoxyethoxy group, a methoxypropoxy group, a methoxybutoxy group, a methoxypentyloxy group, a methoxyhexyloxy group, an ethoxymethoxy group, an ethoxyethoxy group, an ethoxypropoxy group, an ethoxybutoxy group, an ethoxypentyloxy group, an ethoxyhexyloxy group, a propoxymethoxy group, a propoxyethoxy group, a propoxypropoxy group, a propoxybutoxy group, a propoxypentyloxy group, a propoxyhexyloxy group, a butoxymethoxy group, a butoxyethoxy group, a butoxypropoxy group, a butoxybutoxy group, a butoxypentyloxy group, a butoxyhexyloxy group, a pentyloxymethoxy group, a pentyloxyethoxy group, a pentyloxypropoxy group, a pentyloxybutoxy group, a pentyloxypentyloxy group, a pentyloxyhexyloxy group, a hexyloxymethoxy group, a hexyloxyethoxy group, a hexyloxypropoxy group, a hexyloxybutoxy group, a hexyloxypentyloxy group, a hexyloxyhexyloxy group and the like.

[0041]

The "C_{1-6} alkyl-carbonyl group" is an alkyl-carbonyl group wherein the C_{1-6} alkyl moiety is the "C_{1-6} alkyl group" defined above, preferably a straight chain or branched chain alkyl group having 1 to 4 carbon atoms. Examples thereof include a methylcarbonyl group, an ethylcarbonyl group, a propylcarbonyl group, an isopropylcarbonyl group, a butylcarbonyl group, an isobutylcarbonyl group, a sec-butylcarbonyl group, a tert-butylcarbonyl group, a pentylcarbonyl group, an isopentylcarbonyl group, a 1,1-dimethylpropylcarbonyl group, a hexylcarbonyl group and the like.

[0042]

The "C_{1-6} alkyl-sulfonyl group" is an alkyl-sulfonyl group wherein the C_{1-6} alkyl moiety is the "C_{1-6} alkyl group" defined above, preferably a straight chain or branched chain alkyl group having 1 to 4 carbon atoms. Examples thereof include a methylsulfonyl group, an ethylsulfonyl group, a propylsulfonyl group, an isopropylsulfonyl group, a butylsulfonyl group, an isobutylsulfonyl group, a sec-butylsulfonyl group, a tert-butylsulfonyl group, a pentylsulfonyl group, an isopentylsulfonyl group, a 1,1-dimethylpropylsulfonyl group, a hexylsulfonyl group and the like.

[0043]

The "C_{3-8} cycloalkyl group" is a saturated cycloalkyl group having 3 to 8 carbon atoms, preferably 3 to 5 carbon atoms, and examples thereof include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group, a cyclooctyl group and the like.

[0044]

The "C_{3-8} cycloalkane" is saturated cycloalkane having 3 to 8 carbon atoms, preferably 3 to 5 carbon atoms, and examples thereof include cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane and the like.

[0045]

The "hetero ring" means a saturated or unsaturated (including partially unsaturated and completely unsaturated) monocyclic hetero ring containing, besides carbon atom, 1 to 6 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, or a fused ring of the hetero rings, or a fused ring of a carbon ring selected from benzene, cyclopentane and cyclohexane, and the hetero ring.

[0046]

Examples of the above-mentioned "saturated monocyclic hetero ring containing, besides carbon atom, 1 to 6 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom" include a 4- to 7-membered saturated monocyclic hetero ring containing, besides carbon atom, 1 to 6 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and the like. Specific examples thereof include azetidine, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, imidazolidine, pyrazolidine, 1,3-dioxolane, 1,3-oxathioran, oxazolidine, thiazolidine, piperidine, piperazine, tetrahydropyran, tetrahydrothiopyran, dioxane, morpholine, thiomorpholine and the like.

[0047]

Examples of the above-mentioned "unsaturated (including partially unsaturated and completely unsaturated) monocyclic hetero ring containing, besides carbon atom, 1 to 6 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom" include a 4- to 7-membered unsaturated (including partially unsaturated and completely unsaturated) monocyclic hetero ring containing, besides carbon atom, 1 to 6 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and the like. Specific examples thereof include pyrroline, furan, thiophene, imidazole, imidazoline, pyrazole, oxazole, isoxazole, thiazole, isothiazole, 1,2,4-triazole, 1,2,3-triazole, tetrazole, 1,3,4-oxadiazole, 1,2,4-oxadiazole, 1,3,4-thiadiazole, 1,2,4-thiadiazole, furazan, pyridine, pyrimidine, 3,4-dihydropyrimidine, pyridazine, pyrazine,

1,3,5-triazine, pyrazoline, oxazoline, isooxazoline, thiazoline, isothiazoline, pyran and the like.

[0048]

Examples of the above-mentioned "fused ring of the hetero rings, or fused ring of a carbon ring selected from benzene, cyclopentane and cyclohexane, and the hetero ring" include indole, isoindole, benzimidazole, indazole, benzothiazole, benzofuran, isobenzofuran, indolizine, quinoline, isoquinoline, 1,2-dihydroquinoline, quinazoline, quinoxaline, cinnoline, phthalazine, quinolizidine, purine, pteridine, indoline, isoindoline, 5,6,7,8-tetrahydroquinoline, 1,2,3,4-tetrahydroquinoline, 1,3-benzodioxolane, 3,4-methylenedioxypyridine, 4,5-ethylenedioxypyrimidine, chromene, chromane, isochromane, 1,2,4-benzotriazine and the like.

[0049]

The "saturated monocyclic hetero ring" formed by R^a and R^b together with the nitrogen atom bonded thereto means a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and examples thereof include a 4- to 7-membered (e.g., 4- to 6-membered) saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 (e.g., 1 to 3, preferably 1) hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, and the like. Specific examples of the saturated monocyclic hetero ring include those exemplified as the above-mentioned "saturated monocyclic hetero ring containing, beside carbon atom, 1 to 6 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom", which contain, beside carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom.

The saturated monocyclic hetero ring is optionally substituted by the same or different 1 to 5 (e.g., 1 to 3, preferably 1) substituents selected from the following group B.

[0050]

The "saturated monocyclic hetero ring" formed by R^2 and R^3, or R^4 and R^5, together with the carbon atom bonded thereto means a saturated monocyclic hetero ring containing, besides carbon atom, 1 to 6 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and examples thereof include a 5- to 7-membered (e.g., 6-membered) saturated monocyclic hetero ring containing, besides carbon atom, 1 to 6 (e.g., 1 to 3, preferably 1) hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and the like. Specific examples of the saturated monocyclic hetero ring include those similar to the saturated monocyclic hetero rings exemplified as the above-mentioned "saturated monocyclic hetero ring containing, besides carbon atom, 1 to 6 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom".

[0051]

The "saturated monocyclic hetero ring" formed by R^{A1} and R^{A2} together with the nitrogen atom bonded thereto means a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and examples thereof include a 4- to 6-membered saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 3 (e.g., 1) hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom and the like. Specific examples of the saturated monocyclic hetero ring include those exemplified as the above-mentioned "saturated monocyclic hetero ring containing, besides carbon atom, 1 to 6 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom", which optionally contain, besides carbon atom and one nitrogen atom, 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom.

The saturated monocyclic hetero ring is optionally substituted by the same or different 1 to 5 substituents

selected from the following group B.

[0052]

The "hetero ring" formed by R^{A3} and R^{A4} together with the nitrogen atom bonded thereto means a hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and examples thereof include a 4- to 6-membered (e.g., 5-membered) monocyclic hetero ring, a 8- to 10-membered (e.g., 9-membered) fused cyclic hetero ring and the like, optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom. Specific examples of the hetero ring include those exemplified as the above-mentioned "hetero ring", which optionally contain, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom.

The hetero ring is optionally substituted by 1 or 2 oxo groups.

[0053]

The "saturated monocyclic heterocyclic group" for R^1 means a saturated monocyclic heterocyclic group containing, besides carbon atom, 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and examples thereof include a 5- or 6-membered saturated monocyclic heterocyclic group containing, besides carbon atom, 1 to 3 (e.g., 1) hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and the like. Specific examples of the saturated monocyclic heterocyclic group include groups derived from those exemplified as the above-mentioned "saturated monocyclic hetero ring containing, besides carbon atom, 1 to 6 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom", which optionally contain, besides carbon atom, 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom and the like. Examples thereof include a pyrrolidinyl group, a

tetrahydrofuryl (e.g., 3-tetrahydrofuryl) group, a tetrahydrothienyl group, an imidazolidinyl group, a pyrazolidinyl group, a 1,3-dioxolanyl group, a 1,3-oxathioranyl group, an oxazolidinyl group, a thiazolidinyl group, a piperidinyl group, a piperazinyl group, a tetrahydropyranyl group, a tetrahydrothiopyranyl group, a dioxanyl group, a morpholinyl group, a thiomorpholinyl group and the like.

[0054]

The "group A" includes the following substituents (a) to (i).

(a) $-CO-NR^{A1}R^{A2}$

wherein R^{A1} and R^{A2} are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the following group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^{A1} and R^{A2} optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from the following group B,

(b) a hydroxyl group,

(c) a C_{1-6} alkoxy group,

(d) a C_{1-6} alkoxy-C_{1-6} alkoxy group,

(e) a cyano group,

(f) $-NR^{A3}R^{A4}$

wherein R^{A3} and R^{A4} are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group,

(iii) a C_{1-6} alkyl-carbonyl group, or

(iv) a C_{1-6} alkyl-sulfonyl group, or

R^{A3} and R^{A4} optionally form, together with the nitrogen atom bonded thereto, a hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by 1 or 2 oxo groups,

(g) a carboxyl group,

(h) a C_{1-6} alkyl-sulfonyl group, and

(i) a C_{1-6} alkyl-carbonyl group.

[0055]

The "C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A" is that wherein the "C_{1-6} alkyl group" defined above is optionally substituted by the same or different 1 to 5 (e.g., 1 to 3, preferably 1) substituents selected from "group A" defined above, and includes an unsubstituted C_{1-6} alkyl group.

[0056]

The "group B" includes the following substituents (a) to (e).

(a) a hydroxyl group,

(b) a C_{1-6} alkoxy group,

(c) a C_{1-6} alkoxy-C_{1-6} alkyl group,

(d) a C_{3-8} cycloalkyl group, and

(e) an oxo group.

[0057]

The "C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group B" is that wherein the "C_{1-6} alkyl group" defined above is optionally substituted by the same or different 1 to 5 (e.g., 1 to 3, preferably 1) substituents selected from the "group B" defined above, and includes an unsubstituted C_{1-6} alkyl group.

[0058]

The "saturated monocyclic hetero ring is optionally substituted by the same or different 1 to 5 substituents

selected from group B" for R^a and R^b, or R^{A1} and R^{A2} means that the "saturated monocyclic hetero ring" defined above which is formed by R^a and R^b, or R^{A1} and R^{A2} together with the nitrogen atom bonded thereto is optionally substituted by the same or different 1 to 5 (e.g., 1 to 3, preferably 1) substituents selected from the "group B" defined above, and includes an unsubstituted saturated monocyclic hetero ring.

[0059]

In the above-mentioned formula [I], preferable groups are as described below.

[0060]

R^1 is

(1) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from

(i) a C_{3-8} cycloalkyl group, and

(ii) a C_{1-6} alkoxy group,

(2) a C_{3-8} cycloalkyl group, or

(3) a saturated monocyclic heterocyclic group containing, besides carbon atom, 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom.

[0061]

Preferable embodiment of R^1 is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from

(i) a C_{3-8} cycloalkyl group, and

(ii) a C_{1-6} alkoxy group.

More preferable embodiment of R^1 is a C_{1-6} alkyl group.

A different, more preferable embodiment of R^1 is a C_{1-6} alkyl group substituted by a C_{3-8} cycloalkyl group.

[0062]

A different, preferable embodiment of R^1 is a C_{3-8} cycloalkyl group.

[0063]

Further different preferable embodiments of R^1 are

(1) a C_{1-6} alkyl group optionally substituted by the same or

different 1 to 3 C_{3-8} cycloalkyl groups,

(2) a C_{3-8} cycloalkyl group,

(3) a 5- or 6-membered saturated monocyclic heterocyclic group containing, besides carbon atom, 1 to 3 (e.g., 1) hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and the like.

Of these, preferred are a methyl group, a cyclopropylmethyl group, an ethyl group, a 1-cyclopropylethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a 1,2-dimethylpropyl group, a 2,2-dimethylpropyl group, a 1-ethylpropyl group, a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a tetrahydrofuryl (e.g., 3-tetrahydrofuryl) group and the like.

[0064]

R^2, R^3, R^4 and R^5 are the same or different and each is

(1) a hydrogen atom,

(2) a carboxyl group,

(3) $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the above-mentioned group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from the above-mentioned group B,

(4) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the above-mentioned group A, or

(5) a cyano group.

[0065]

In a preferable embodiment of R^2, R^3, R^4 and R^5, one of R^2, R^3, R^4 and R^5 is $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the above-mentioned group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from the above-mentioned group B.

[0066]

In another preferable embodiment of R^2, R^3, R^4 and R^5, one of R^2, R^3, R^4 and R^5 is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the above-mentioned group A.

[0067]

Further preferable embodiments of R^2, R^3, R^4 and R^5 are respectively shown below.

[0068]

As R^2, preferred are

(1) a hydrogen atom,

(2) a carboxyl group,

(3) $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom, and

(ii) a C_{1-6} alkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a 4- to 7-membered (e.g., 4- to 6-

membered) saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 (e.g., 1 to 3, preferably 1) hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom,

(4) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 3 (e.g., 1) substituents selected from

(a) $-CO-NR^{A1}R^{A2}$

wherein R^{A1} and R^{A2} are the same or different and each is

(i) a hydrogen atom, or

(ii) a C_{1-6} alkyl group,

(b) a hydroxyl group,

(c) a C_{1-6} alkoxy group,

(d) a C_{1-6} alkoxy-C_{1-6} alkoxy group,

(e) a cyano group,

(f) $-NR^{A3}R^{A4}$

wherein R^{A3} and R^{A4} are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group,

(iii) a C_{1-6} alkyl-carbonyl group, or

(iv) a C_{1-6} alkyl-sulfonyl group, and

(g) a carboxyl group, and

(5) a cyano group.

As R^2, more preferred are

(1) a hydrogen atom,

(2) a carboxyl group,

(3) $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a methyl group,

(ii') an ethyl group,

(ii") an isopropyl group, or

(ii"') a tert-butyl group, or

R^a and R^b optionally form, together with the nitrogen

atom bonded thereto, a saturated monocyclic hetero ring selected from azetidine, pyrrolidine and morpholine,

(4) a methyl group, an ethyl group, a propyl goroup, or an isopropyl group, which is optionally substituted by the same or different 1 to 3 (e.g., 1) substituents selected from

(a) $-CO-NR^{A1}R^{A2}$

wherein R^{A1} and R^{A2} are the same or different and each is

(i) a hydrogen atom, or

(ii) a methyl group,

(b) a hydroxyl group,

(c) a methoxy group,

(c') an ethoxy group,

(c'') an isopropoxy group,

(d) a methoxyethoxy group,

(e) a cyano group,

(f) $-NR^{A3}R^{A4}$

wherein R^{A3} and R^{A4} are the same or different and each is a hydrogen atom, a methyl group, a methylcarbonyl group, an isopropylcarbonyl group, a tert-butylcarbonyl group, a 1,1-dimethylpropylcarbonyl group or a methylsulfonyl group, and

(g) a carboxyl group, and

(5) a cyano group.

[0069]

As R^3, preferred are

(1) a hydrogen atom, and

(2) a C_{1-6} alkyl group optionally substituted by a C_{1-6} alkoxy group.

As R^3, more preferred are a hydrogen atom, a methyl group and a methoxymethyl group.

[0070]

As R^4, preferred are

(1) a hydrogen atom,

(2) a carboxyl group,

(3) $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 (e.g., 1 to 3, preferably 1) substituents selected from a C_{1-6} alkoxy group and a C_{3-8} cycloalkyl group, or

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring which is a 4- to 7-membered (e.g., 4- to 6-membered) saturated monocyclic hetero ring which is optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 (e.g., 1 to 3, preferably 1) hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 (e.g., 1 to 3, preferably 1) substituents selected from (a) a hydroxyl group, (b) a C_{1-6} alkoxy group, (c) a C_{1-6} alkoxy-C_{1-6} alkyl group and (d) an oxo group,

(4) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 (e.g., 1 to 3, preferably 1) substituents

(a) $-CO-NR^{A1}R^{A2}$

wherein R^{A1} and R^{A2} are the same or different and each is selected from

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 (e.g., 1 to 3, preferably 1) C_{1-6} alkoxy groups, or

(iii) a C_{3-8} cycloalkyl group, or

R^{A1} and R^{A2} optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring which is a 4- to 6-membered saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 3 (e.g., 1) hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by a C_{1-6} alkoxy group,

(b) a hydroxyl group,

(c) a C_{1-6} alkoxy group,

(d) a C_{1-6} alkoxy-C_{1-6} alkoxy group,

(e) a cyano group,

(f) $-NR^{A3}R^{A4}$

wherein R^{A3} and R^{A4} are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group,

(iii) a C_{1-6} alkyl-carbonyl group, or

(iv) a C_{1-6} alkyl-sulfonyl group, or

R^{A3} and R^{A4} optionally form, together with the nitrogen atom bonded thereto, a hetero ring which is a 4- to 7-membered (e.g., 6-membered) monocyclic hetero ring, or a 8- to 10-membered (e.g., 9-membered) fused cyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by 1 or 2 oxo groups,

(g) a carboxyl group,

(h) a C_{1-6} alkyl-sulfonyl group, and

(i) a C_{1-6} alkyl-carbonyl group, and

(5) a cyano group.

As R^4, more preferred are

(1) a hydrogen atom,

(2) a carboxyl group,

(3) $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a methyl group, an ethyl group, an isopropyl group or an isobutyl group, which is optionally substituted by the same or different one substituent selected from a methoxy group and a cyclopropyl group, or

(iii) a cyclopropyl group, or

R^a and R^b optionally form, together with the nitrogen

atom bonded thereto, a saturated monocyclic hetero ring selected from azetidine, pyrrolidine, piperidine and morpholine, which is optionally substituted by one substituent selected from a hydroxyl group, a methoxy group, a methoxymethyl group and an oxo group,

(4) a methyl group, an ethyl group, a propyl group, an isopropyl group or a tert-butyl group, which is optionally substituted by one or two substituents selected from

(a) $-CO-NR^{A1}R^{A2}$

wherein R^{A1} and R^{A2} are the same or different and each is

(i) a hydrogen atom,

(ii) a methyl group, an ethyl group, an isopropyl group or an isobutyl group, which is optionally substituted by a methoxy group, or

(iii) a cyclopropyl group, or

R^{A1} and R^{A2} optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring selected from azetidine, piperidine and morpholine, and optionally substituted by a methoxy group,

(b) a hydroxyl group,

(c) a methoxy group,

(c') an ethoxy group,

(c") a propoxy group,

(c"') an isopropoxy group,

(c"") a butoxy group,

(d) a methoxyethoxy group,

(d') an ethoxyethoxy group,

(d") a methoxypropoxy group,

(d"') a methoxyisopropoxy group,

(d"") an isopropoxyethoxy group,

(e) a cyano group,

(f) $-NR^{A3}R^{A4}$

wherein R^{A3} and R^{A4} are the same or different and each is a hydrogen atom, a methyl group, an ethyl group, an

isopropyl group, a methylcarbonyl group, an ethylcarbonyl group, an isopropylcarbonyl group, a methylsulfonyl group or a tert-butylsulfonyl group, or

R^{A3} and R^{A4} optionally form, together with the nitrogen atom bonded thereto, pyrazole, triazole (e.g., 1,2,4-triazole), tetrazole, oxazolidine or isoindoline, which is optionally substituted by 1 or 2 oxo groups,

(g) a carboxyl group,

(h) a methylsulfonyl group, and

(i) a methylcarbonyl group, and

(5) a cyano group.

[0071]

As R^5, preferred are a hydrogen atom and a C_{1-6} alkyl group optionally substituted by one substituent selected from a C_{1-6} alkoxy group and a C_{1-6} alkoxy-C_{1-6} alkoxy group.

As R^5, more preferred are a hydrogen atom and a methyl group or an ethyl group, which is optionally substituted by one substituent selected from a methoxy group and a methoxyethoxy group.

[0072]

R^2 and R^3, or R^4 and R^5 optionally form, together with the carbon atom bonded thereto, i) C_{3-8} cycloalkane or ii) a saturated monocyclic hetero ring containing, besides carbon atom, 1 to 6 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom.

As the ring formed by R^2 and R^3, or R^4 and R^5 together with the carbon atom bonded thereto, preferred are

i) C_{3-8} cycloalkane, and

ii) a 5- to 7-membered (e.g., 6-membered) saturated monocyclic hetero ring containing, besides carbon atom, 1 to 6 (e.g., 1 to 3, preferably 1) hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom.

As the ring formed by R^2 and R^3, or R^4 and R^5 together with the carbon atom bonded thereto, more preferred are cyclopropane and tetrahydropyran.

[0073]

Here, R^2, R^3, R^4 and R^5 are not hydrogen atoms at the same time.

[0074]

R^6 is

(1) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 (e.g., 1 to 3) halogen atoms,

(2) a C_{1-6} alkoxy group,

(3) a halogen atom, or

(4) a C_{3-8} cycloalkyl group.

As R^6, preferred is a halogen atom.

Other preferable embodiments of R^6 are a methyl group, a trifluoromethyl group, a methoxy group, an ethoxy group, a fluorine atom, a chlorine atom, a bromine atom and a cyclopropyl group.

[0075]

Y is

(1) CH, or

(2) a nitrogen atom.

As Y, preferred is CH.

Other preferable embodiment of Y is a nitrogen atom.

[0076]

m is an integer of 1 to 5, and when m is an integer of 2 to 5, the above-mentioned R^6 may be the same or different.

As m, preferred is 1 to 3.

As m, more preferred is 1 or 2.

[0077]

n is an integer of 1 to 3.

As n, preferred is 1.

[0078]

In the above-mentioned formula [I-1], preferable groups are as described below.

[0079]

R^{11} is

(1) a C_{1-6} alkyl group optionally substituted by the same or

different 1 to 5 substituents selected from

(i) a C_{3-8} cycloalkyl group, and

(ii) a C_{1-6} alkoxy group, or

(2) a C_{3-8} cycloalkyl group.

As R^{11}, those exemplified as the preferable embodiments of R^1 in the above-mentioned formula (I), which are within the scope of R^{11}, are preferable.

[0080]

R^{21}, R^{31}, R^{41} and R^{51} are the same or different and each is

(1) a hydrogen atom,

(2) $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the above-mentioned group B, and

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from the above-mentioned group B, or

(3) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the above-mentioned group A.

[0081]

As R^{21}, preferred is a hydrogen atom.

Other preferable embodiment of R^{21} is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the above-mentioned group A. More preferred is a C_{1-6} alkyl group.

Examples of yet other preferable embodiment of R^{21} include those exemplified as the preferable embodiments of R^2

in the above-mentioned formula (I), which are within the scope of R^{21}.

[0082]

As R^{31}, preferred is a hydrogen atom.

Examples of other preferable embodiment of R^{31} include those exemplified as the preferable embodiments of R^3 in the above-mentioned formula (I), which are within the scope of R^{31}.

[0083]

As R^{41}, preferred is a hydrogen atom.

Other preferable embodiment of R^{41} is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the above-mentioned group A. More preferred is a C_{1-6} alkyl group.

Examples of yet other preferable embodiment of R^{41} include those exemplified as the preferable embodiments of R^4 in the above-mentioned formula (I), those contained within the scope of R^{41}.

[0084]

As R^{51}, preferred is a hydrogen atom.

Other preferable embodiments of R^{51} are those exemplified as the preferable embodiments of R^5 in the above-mentioned formula (I), which are within the scope of R^{51}.

[0085]

Here, R^{21}, R^{31}, R^{41} and R^{51} are not hydrogen atoms at the same time.

[0086]

R^{61} is a halogen atom.

As R^{61}, preferred are a fluorine atom and a chlorine atom.

[0087]

R^{62} is a hydrogen atom or a halogen atom.

As R^{62}, preferred are a hydrogen atom, a fluorine atom and a bromine atom.

[0088]

In the above-mentioned formula [I-2], preferable groups are as described below.

[0089]

R^{12} is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from

(i) a C_{3-8} cycloalkyl group, and

(ii) a C_{1-6} alkoxy group.

As R^{12}, those exemplified as the preferable embodiments of R^1 in the above-mentioned formula (I), which are within the scope of R^{12}, are preferable.

[0090]

R^{22}, R^{32}, R^{42} and R^{52} are the same or different and each is

(1) a hydrogen atom,

(2) $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the above-mentioned group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from the above-mentioned group B, or

(3) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the above-mentioned group A.

[0091]

As R^{22}, preferred is a hydrogen atom.

Other preferable embodiments of R^{22} are those exemplified as the preferable embodiments of R^2 in the above-mentioned formula (I), which are within the scope of R^{22}.

[0092]

As R^{32}, preferred is a hydrogen atom.

Other preferable embodiments of R^{32} are those exemplified as the preferable embodiments of R^3 in the above-mentioned formula (I), which are within the scope of R^{32}.

[0093]

As R^{42}, preferred is $-CO-NR^aR^b$

wherein R^a and R^b form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from the above-mentioned group B.

Other preferable embodiments of R^{42} are those exemplified as the preferable embodiments of R^4 in the above-mentioned formula (I), which are within the scope of R^{42}.

[0094]

As R^{52}, preferred is a C_{1-6} alkyl group.

Other preferable embodiments of R^{52} are those exemplified as the preferable embodiments of R^5 in the above-mentioned formula (I), which are within the scope of R^{52}.

[0095]

Here, R^{22}, R^{32}, R^{42} and R^{52} are not hydrogen atoms at the same time.

[0096]

R^{63} is a halogen atom.

As R^{63}, preferred is a fluorine atom.

[0097]

R^{64} is a hydrogen atom or a halogen atom.

As R^{64}, preferred are a hydrogen atom and a fluorine atom.

[0098]

As the compound of the present invention, compounds represented by the above-mentioned formula [I], the formula [I-1] and the formula [I-2], and compounds described in the following Examples are preferable.

[0099]

A pharmaceutically acceptable salt of the "compounds represented by the above-mentioned formula [I], the formula [I-1] and the formula [I-2]" (hereinafter to be also referred to as the compound of the present invention) may be any salt as long as it forms an atoxic salt with the compound of the present invention. Examples thereof include a salt with an inorganic acid, a salt with an organic acid, a salt with an inorganic base, a salt with an organic base, a salt with an amino acid and the like.

Examples of the salt with an inorganic acid include salts with hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, hydrobromic acid and the like.

Examples of the salt with an organic acid include salts with oxalic acid, malonic acid, maleic acid, citric acid, fumaric acid, lactic acid, malic acid, succinic acid, tartaric acid, acetic acid, trifluoroacetic acid, gluconic acid, ascorbic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

Examples of the salt with an inorganic base include sodium salt, potassium salt, calcium salt, magnesium salt, ammonium salt and the like.

Examples of the salt with an organic base include salts with methylamine, diethylamine, trimethylamine, triethylamine, ethanolamine, diethanolamine, triethanolamine, ethylenediamine, tris(hydroxymethyl)methylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, guanidine, pyridine, picoline, choline, cinchonine, meglumine and the like.

Examples of the salt with an amino acid include salts with lysine, arginine, aspartic acid, glutamic acid and the like.

[0100]

Each salt can be obtained by reacting a compound represented by the formula [I], the formula [I-1] and the formula [I-2] with an inorganic base, an organic base, an

inorganic acid, an organic acid or an amino acid according to a method known per se.

[0101]

In the present invention, as the pharmaceutically acceptable salt of the compounds represented by the formula [I], the formula [I-1] and the formula [I-2], preferred are salts with hydrochloric acid (e.g., 1 hydrochloride, 2 hydrochloride), salts with hydrobromic acid (e.g., 1 hydrobromide, 2 hydrobromide), and sodium salt.

[0102]

The "solvate" is a compound represented by the formula [I], the formula [I-1] and the formula [I-2] or a pharmaceutically acceptable salt thereof, with which a molecule of a solvent is coordinated, and also encompasses hydrates (also referred to as water-containing compound). The solvate is preferably a pharmaceutically acceptable solvate, such as a 1 hydrate, a 1/2 hydrate, a 2 hydrate, a 1 hydrate of sodium salt, a 1 methanolate, a 1 ethanolate, a 1 acetonitrilate, a 2/3 ethanolate of 2 hydrochloride of the compound represented by the formula [I], the formula [I-1] and the formula [I-2] and the like.

[0103]

A solvate of a compound represented by the formula [I], the formula [I-1] and the formula [I-2] or a pharmaceutically acceptable salt thereof can be obtained according to a method known per se.

[0104]

In addition, there can be various isomers of compounds represented by the above-mentioned formulas [I], [I-1] and [I-2]. For example, when E form and Z form are present as geometric isomers, and when an asymmetric carbon atom is present, enantiomers and diastereomers are present as stereo isomers based on them. In addition, when axial chirality is present, stereo isomers based thereon are present. Where necessary, tautomers can be present. Accordingly, all of such

isomers and mixtures thereof are encompassed in the scope of the present invention. As the compound of the present invention, one isolated and purified from various isomers, by-products, metabolites or prodrugs is preferable, and one having a purity of not less than 90% is preferable and one having a purity of not less than 95% is more preferable.

[0105]

In addition, the compounds represented by the formula [I], the formula [I-1] and the formula [I-2] may be crystal or amorphous.

[0106]

In addition, a compound represented by the formula [I], the formula [I-1] and the formula [I-2] may be labeled with an isotope (e.g., ^{3}H, ^{14}C, ^{35}S etc.).

[0107]

As the compounds represented by the formula [I], the formula [I-1] and the formula [I-2] or a pharmaceutically acceptable salt thereof, or a solvate thereof, compounds represented by the formula [I], the formula [I-1] and the formula [I-2] or a pharmaceutically acceptable salt thereof, or a solvate thereof, which is substantially purified, is preferable. More preferred is compounds represented by the formula [I], the formula [I-1] and the formula [I-2] or a pharmaceutically acceptable salt thereof, or a solvate thereof, which has been purified to a purity of not less than 80%.

[0108]

In the present invention, a prodrug of a compound represented by the formula [I], the formula [I-1] and the formula [I-2] can also be a useful medicament.

[0109]

A "prodrug" is a derivative of the compound of the present invention, which has a chemically or metabolically decomposable group and which restores to the original compound to show its inherent efficacy after administration to the body by, for example, hydrolysis, solvolysis or decomposition under

physiological conditions. It includes a complex and a salt, not involving a covalent bond.

[0110]

The prodrug is utilized, for example, for improving absorption by oral administration or targeting of a target site.

[0111]

Examples of the site to be modified include highly reactive functional groups in the compound of the present invention, such as hydroxyl group, carboxyl group, amino group and the like.

[0112]

Examples of the hydroxyl-modifying group include acetyl group, propionyl group, isobutyryl group, pivaloyl group, palmitoyl group, benzoyl group, 4-methylbenzoyl group, dimethylcarbamoyl group, dimethylaminomethylcarbonyl group, sulfo group, alanyl group, fumaryl group and the like. In addition, a sodium salt of 3-carboxybenzoyl group, 2-carboxyethylcarbonyl group and the like can also be used.

Examples of the carboxyl-modifying group include methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, tert-butyl group, pivaloyloxymethyl group, carboxymethyl group, dimethylaminomethyl group, 1-(acetyloxy)ethyl group, 1-(ethoxycarbonyloxy)ethyl group, 1-(isopropyloxycarbonyloxy)ethyl group, 1-(cyclohexyloxycarbonyloxy)ethyl group, (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl group, benzyl group, phenyl group, o-tolyl group, morpholinoethyl group, N,N-diethylcarbamoylmethyl group, phthalidyl group and the like.

Examples of the amino-modifying group include hexylcarbamoyl group, 3-methylthio-1-(acetylamino)propylcarbonyl group, 1-sulfo-1-(3-ethoxy-4-hydroxyphenyl)methyl group, (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl group and the like.

[0113]

Examples of the "pharmaceutical composition" include oral preparations such as tablet, capsule, granule, powder, troche, syrup, emulsion, suspension and the like, and parenteral agents such as external preparation, suppository, injection, eye drop, transnasal agent, pulmonary preparation and the like.

[0114]

The pharmaceutical composition of the present invention (e.g., an anti-HIV composition, a pharmaceutical composition for HIV integrase inhibitory etc.) is produced by appropriately admixing a suitable amount of a compound represented by the formula [I], the formula [I-1] or the formula [I-2] of the present invention or a salt thereof, or a solvate thereof with at least one kind of a pharmaceutically acceptable carrier according to a method known per se in the technical field of pharmaceutical preparations. The content of the compound represented by the formula [I], the formula [I-1] or the formula [I-2] of the present invention or a salt thereof, or a solvate thereof in the pharmaceutical composition varies depending on the dosage form, the dose and the like, and the like. It is, for example, 0.1 to 100 wt% of the whole composition.

Examples of the "pharmaceutically acceptable carrier" include various organic or inorganic carrier substances conventionally used as preparation materials such as excipient, disintegrant, binder, fluidizer, lubricant and the like for solid dosage forms, and solvent, solubilizing agent, suspending agent, isotonicity agent, buffering agent, soothing agent and the like for liquid preparations. Where necessary, additives such as preservative, antioxidant, colorant, sweetening agent and the like are used.

Examples of the "excipient" include lactose, sucrose, D-mannitol, D-solbitol, cornstarch, dextrin, microcrystalline cellulose, crystalline cellulose, carmellose, carmellose calcium, sodium carboxymethyl starch, low-substituted hydroxypropylcellulose, gum arabic and the like.

Examples of the "disintegrant" include carmellose, carmellose calcium, carmellose sodium, sodium carboxymethyl starch, croscarmellose sodium, crospovidone, low-substituted hydroxypropylcellulose, hydroxypropylmethylcellulose, crystalline cellulose and the like.

Examples of the "binder" include hydroxypropylcellulose, hydroxypropylmethylcellulose, povidone, crystalline cellulose, sucrose, dextrin, starch, gelatin, carmellose sodium, gum arabic and the like.

Examples of the "fluidizer" include light anhydrous silicic acid, magnesium stearate and the like.

Examples of the "lubricant" include magnesium stearate, calcium stearate, talc and the like.

Examples of the "solvent" include purified water, ethanol, propylene glycol, macrogol, sesame oil, corn oil, olive oil and the like.

Examples of the "solubilizing agent" include propylene glycol, D-mannitol, benzyl benzoate, ethanol, triethanolamine, sodium carbonate, sodium citrate and the like.

Examples of the "suspending agent" include benzalkonium chloride, carmellose, hydroxypropylcellulose, propylene glycol, povidone, methylcellulose, glycerol monostearate and the like.

Examples of the "isotonicity agent" include glucose, D-sorbitol, sodium chloride, D-mannitol and the like.

Examples of the "buffering agent" include sodium hydrogen phosphate, sodium acetate, sodium carbonate, sodium citrate and the like.

Examples of the "soothing agent" include benzyl alcohol and the like.

Examples of the "preservative" include ethyl parahydroxybenzoate, chlorobutanol, benzyl alcohol, sodium dehydroacetate, sorbic acid and the like.

Examples of the "antioxidant" include sodium sulfite, ascorbic acid and the like.

Examples of the "colorant" include food colors (e.g.,

Food Color Red No. 2 or 3, Food Color yellow 4 or 5 etc.), β-carotene and the like.

Examples of the "sweetening agent" include saccharin sodium, dipotassium glycyrrhizinate, aspartame and the like.

[0115]

The pharmaceutical composition of the present invention can be administered not only to human but also to mammals other than human (e.g., mouse, rat, hamster, guinea pig, rabbit, cat, dog, swine, bovine, horse, sheep, monkey etc.) orally or parenterally (e.g., topical, rectal, intravenous administration etc.). While the dose varies depending on the subject of administration, disease, symptom, dosage form, administration route and the like, for example, the dose for oral administration to an adult patient (body weight: about 60 kg) is generally within the scope of about 1 mg to 1 g per day, based on the compound of the present invention as an active ingredient. The amount can be administered in one to several portions.

[0116]

The compounds represented by the above-mentioned formula [I], the formula [I-1] and the formula [I-2] or a pharmaceutically acceptable salt thereof, or a solvate thereof inhibits HIV integrase, and can be used as an active ingredient of a therapeutic agent or prophylactic agent for HIV infection.

To "inhibit HIV integrase" means to specifically inhibit the function as HIV integrase to eliminate or attenuate the activity thereof. For example, it means to specifically inhibit the function of HIV integrase under the conditions of the below-mentioned Experimental Example 1. As the "inhibition of HIV integrase", preferred is "inhibition of human HIV integrase". As the "HIV integrase inhibitor", preferred is a "human HIV integrase inhibitor".

The compounds represented by the above-mentioned formula [I], the formula [I-1] and the formula [I-2] or a

pharmaceutically acceptable salt thereof, or a solvate thereof can be used in combination (hereinafter to be referred to as combination use) with other single or plural medicaments (hereinafter to be also referred to as a concomitant drug) by a conventional method generally employed in the medicament field.

The administration frequency of the compounds represented by the above-mentioned formula [I], the formula [I-1] and the formula [I-2], or a pharmaceutically acceptable salt thereof, or a solvate thereof, and a concomitant drug is not limited, and they may be administered as a combined agent to the subject of administration, or the two may be administered simultaneously or at certain time intervals. In addition, they may be used as a medicament in the form of a kit containing the pharmaceutical composition of the present invention and a concomitant drug. The dose of the concomitant drug may be determined according to the dosage used clinically, and can be appropriately determined depending on the subject of administration, disease, symptom, dosage form, administration route, administration time, combination and the like. The administration form of the concomitant drug is not particularly limited, and the compound of the present invention or a salt thereof, or a solvate thereof and the concomitant drug need only be combined.

[0117]

An anti-HIV agent is generally required to sustain its effect for a long time, so that can be effective not only for temporal suppression of viral growth but also prohibition of viral re-growth. This means that a prolonged administration is necessary and that a high single dose may be frequently inevitable to sustain effect for a longer period through the night. Such prolonged and high dose administration increases the risk of causing side effects.

[0118]

In view of this, one of the preferable embodiments of the

compound of the present invention is such compound permitting high absorption by oral administration, and such compound capable of maintaining blood concentration of the administered compound for an extended period of time.

[0119]

In addition to the above-mentioned, preferable embodiments of the compound of the present invention are a compound having fine pharmacological activity (e.g., a compound having strong HIV integrase inhibitory activity, a compound having high anti-HIV activity), a compound having fine bioavailability (e.g., a compound having high cellular membrane permeability, a compound stable to metabolic enzyme, a compound with low binding ability to protein and the like), a compound having an anti-HIV activity against HIV having G140S/Q148H mutation, and the like.

[0120]

Of the compounds of the present invention, a compound having high pharmacological activity (concretely, IC_{50} of HIV integrase inhibitory activity is less than 0.1 μM, preferably less than 0.01 μM) and high oral absorption, whose blood concentration is maintained for a long time after administration, is more preferable.

[0121]

Using the above-mentioned compound, dose and/or frequency of administration of the compound of the present invention to human are/is expected to be decreased. Preferable administration frequency is not more than twice a day, more preferably, not more than once a day (e.g., once a day, once in two days, etc.).

[0122]

The compound of the present invention can be used for the improvement of viremia due to HIV and/or maintenance of improved condition thereof, prophylaxis and treatment of virus infections, particularly, an HIV infection and/or maintenance of improved condition thereof.

[0123]

As an index of the "treatment", "improvement" or "effect", a decrease in the virus level or HIV RNA level in the body, particularly in blood, can be used.

[0124]

The "prophylaxis of HIV infection" includes administration of a medicament to a person with suspected or possible HIV infection (infection due to transfusion, infection from mother to child), and the like.

[0125]

By the "prophylaxis of AIDS" is meant, for example, administration of a medicament to an individual who tested HIV positive but has not yet developed the disease state of AIDS; administration of a medicament to an individual who shows an improved disease state of AIDS after treatment but who carries HIV still to be eradicated and whose relapse of AIDS is worried; administration of a medicament before infection with HIV out of a fear of possible infection; and the like.

[0126]

Examples of the "other anti-HIV agents" and "other anti-HIV active substances" to be used for a multiple drug combination therapy include an anti-HIV antibody or other antibody, an HIV vaccine or other vaccine, immunostimulants such as interferon, interferon agonist and the like, a ribozyme against HIV, an HIV antisense drug, an HIV reverse transcriptase inhibitor, an HIV protease inhibitor, an HIV integrase inhibitor, an inhibitor of attachment between a receptor (CD4, CXCR4, CCR5 and the like) of a host cell recognized by virus and the virus (CCR5 antagonist and the like), a DNA polymerase inhibitor or DNA synthesis inhibitor, a medicament acting on HIVp24, an HIV fusion inhibitor, an IL-2 agonist or antagonist, a TNF-α antagonist, an α-glucosidase inhibitor, a purine nucleoside phosphorylase inhibitor, an apoptosis agonist or inhibitor, a cholinesterase inhibitor, an immunomodulator and the like.

[0127]

Specific examples of the HIV reverse transcriptase inhibitor include Retrovir(R) (zidovudine), Epivir(R) (lamivudine), Zerit(R) (sanilvudine), Videx(R) (didanosine), Hivid(R) (zalcitabine), Ziagen(R) (abacavir sulfate), Viramune(R) (nevirapine), Stocrin(R) (efavirenz), Rescriptor(R) (delavirdine mesylate), Combivir(R) (zidovudine+lamivudine), Trizivir(R) (abacavir sulfate+lamivudine+zidovudine), Coactinon(R) (emivirine), Phosphonovir(R), Coviracil(R), alovudine (3'-fluoro-3'-deoxythymidine), Thiovir (thiophosphonoformic acid), Capravirin (5-[(3,5-dichlorophenyl)thio]-4-isopropyl-1-(4-pyridylmethyl)imidazole-2-methanol carbamic acid), Tenofovir disoproxil fumarate ((R)-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid bis(isopropoxycarbonyloxymethyl)ester fumarate), DPC-083 ((4S)-6-chloro-4-[(1E)-cyclopropylethenyl]-3,4-dihydro-4-trifluoromethyl-2(1H)-quinazolinone), DPC-961 ((4S)-6-chloro-4-(cyclopropylethynyl)-3,4-dihydro-4-(trifluoromethyl)-2(1H)-quinazolinone), DAPD ((-)-β-D-2,6-diaminopurine dioxolane), Immunocal, MSK-055, MSA-254, MSH-143, NV-01, TMC-120, DPC-817, GS-7340, TMC-125, SPD-754, D-A4FC, capravirine, UC-781, emtricitabine, alovudine, Phosphazid, BCH-10618, DPC-083, Etravirine, BCH-13520, MIV-210, Abacavir sulfate/lamivudine, GS-7340, GW-5634, GW-695634, TMC-278 and the like, wherein (R) means a registered trademark (hereinafter the same) and the names of other medicaments are general names.

[0128]

Specific examples of the HIV protease inhibitor include Crixivan(R) (indinavir sulfate ethanolate), saquinavir, Invirase(R) (saquinavir mesylate), Norvir(R) (ritonavir), Viracept(R) (nelfinavir mesylate), lopinavir, Prozei(R) (amprenavir), Kaletra(R) (ritonavir+lopinavir), mozenavir dimesylate ([4R-(4α,5α,6β)]-1,3-bis[(3-aminophenyl)methyl]-hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2H-1,3-diazepin-

2-one dimethanesulfonate), tipranavir (3'-[(1R)-1-[(6R)-5,6-dihydro-4-hydroxy-2-oxo-6-phenylethyl-6-propyl-2H-pyran-3-yl]propyl]-5-(trifluoromethyl)-2-pyridinesulfonamide), lasinavir (N-[5(S)-(tert-butoxycarbonylamino)-4(S)-hydroxy-6-phenyl-2(R)-(2,3,4-trimethoxybenzyl)hexanoyl]-L-valine 2-methoxyethylenamide), KNI-272 ((R)-N-tert-butyl-3-[(2S,3S)-2-hydroxy-3-N-[(R)-2-N-(isoquinolin-5-yloxyacetyl)amino-3-methylthiopropanoyl]amino-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide), GW-433908, TMC-126, DPC-681, buckminsterfullerene, MK-944A (MK944 (N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-[4-(2-benzo[b]furanylmethyl)-2(S)-(tert-butylcarbamoyl)piperazin-1-yl]pentanamide)+indinavir sulfate), JE-2147 ([2(S)-oxo-4-phenylmethyl-3(S)-[(2-methyl-3-oxy)phenylcarbonylamino]-1-oxabutyl]-4-[(2-methylphenyl)methylamino]carbonyl-4(R)-5,5-dimethyl-1,3-thiazole), BMS-232632 (dimethyl (3S,8S,9S,12S)-3,12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedicarboxylate), DMP-850 ((4R,5S,6S,7R)-1-(3-amino-1H-indazol-5-ylmethyl)-4,7-dibenzyl-3-butyl-5,6-dihydroxyperhydro-1,3-diazepin-2-one), DMP-851, RO-0334649, Nar-DG-35, R-944, VX-385, TMC-114, Tipranavir, Fosamprenavir sodium, Fosamprenavir calcium, Darunavir, GW-0385, R-944, RO-033-4649, AG-1859 and the like.

[0129]

The HIV integrase inhibitor is exemplified by S-1360, L-870810 and the like, the DNA polymerase inhibitor or DNA synthesis inhibitor is exemplified by Foscavir(R), ACH-126443 (L-2',3'-didehydro-dideoxy-5-fluorocytidine), entecavir ((1S,3S,4S)-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]guanine), calanolide A ([10R-(10α,11β,12α)]-11,12-dihydro-12-hydroxy-6,6,10,11-tetramethyl-4-propyl-2H,6H,10H-benzo[1,2-b:3,4-b':5,6-b"]tripyran-2-one), calanolide B, NSC-674447 (1,1'-azobisformamide), Iscador (viscum alubm extract), Rubitecan and the like, the HIV

antisense drug is exemplified by HGTV-43, GEM-92 and the like, the anti-HIV antibody or other antibody is exemplified by NM-01, PRO-367, KD-247, Cytolin(R), TNX-355 (CD4 antibody), AGT-1, PRO-140 (CCR5 antibody), Anti-CTLA-4MAb and the like, the HIV vaccine or other vaccine is exemplified by ALVAC(R), AIDSVAX(R), Remune(R), HIV gp41 vaccine, HIV gp120 vaccine, HIV gp140 vaccine, HIV gp160 vaccine, HIV p17 vaccine, HIV p24 vaccine, HIV p55 vaccine, AlphaVax Vector System, canarypox gp160 vaccine, AntiTat, MVA-F6 Nef vaccine, HIV rev vaccine, C4-V3 peptide, p2249f, VIR-201, HGP-30W, TBC-3B, PARTICLE-3B, Antiferon (interferon-α vaccine) and the like, the interferon or interferon agonist is exemplified by Sumiferon(R), MultiFeron(R), interferon-τ, Reticulose, human leukocyte interferon α and the like, the CCR5 antagonist is exemplified by SCH-351125 and the like, the medicament acting on HIV p24 is exemplified by GPG-NH2 (glycyl-prolyl-glycinamide) and the like, the HIV fusion inhibitor is exemplified by FP-21399 (1,4-bis[3-[(2,4-dichlorophenyl)carbonylamino]-2-oxo-5,8-disodium sulfonyl]naphthyl-2,5-dimethoxyphenyl-1,4-dihydrazone), T-1249, Synthetic Polymeric Construction No3, pentafuside, FP-21399, PRO-542, Enfuvirtide and the like, the IL-2 agonist or antagonist is exemplified by interleukin-2, Imunace(R), Proleukin(R), Multikine(R), Ontak(R) and the like, the TNF-α antagonist is exemplified by Thalomid(R) (thalidomide), Remicade(R) (infliximab), curdlan sulfate and the like, the α-glucosidase inhibitor is exemplified by Bucast(R) and the like, the purine nucleoside phosphorylase inhibitor is exemplified by peldesine (2-amino-4-oxo-3H,5H-7-[(3-pyridyl)methyl]pyrrolo[3,2-d]pyrimidine) and the like, the apoptosis agonist or inhibitor is exemplified by Arkin Z(R), Panavir(R), Coenzyme Q10 (2-deca(3-methyl-2-butenylene)-5,6-dimethoxy-3-methyl-p-benzoquinone) and the like, the cholinesterase inhibitor is exemplified by Cognex(R) and the like, and the immunomodulator is exemplified by Imunox(R), Prokine(R), Met-enkephalin (6-de-L-arginine-7-de-L-arginine-8-

de-L-valinamide-adrenorphin), WF-10 (10-fold dilute tetrachlorodecaoxide solution), Perthon, PRO-542, SCH-D, UK-427857, AMD-070, AK-602, TK-303 (Elvitegravir) and the like.

[0130]

In addition, Neurotropin(R), Lidakol(R), Ancer 20(R), Ampligen(R), Anticort(R), Inactivin(R), PRO-2000, Rev M10 gene, HIV specific cytotoxic T cell (CTL immunotherapy, ACTG protocol 080 therapy, CD4-ζ gene therapy), SCA binding protein, RBC-CD4 complex, Motexafin gadolinium, GEM-92, CNI-1493, (±)-FTC, Ushercell, D2S, BufferGel(R), VivaGel(R), Glyminox vaginal gel, sodium lauryl sulfate, 2F5, 2F5/2G12, VRX-496, Ad5gag2, BG-777, IGIV-C, BILR-255 and the like are exemplified.

[0131]

The compound of the present invention can be combined with one or more (e.g., 1 or 2) kinds of other anti-HIV active substances (to be also referred to as other anti-HIV agents), and used as an anti-HIV agent and the like for the prophylaxis or treatment of HIV infection. As the "other anti-HIV agents" and "other anti-HIV active substances" to be used for a multiple drug combination therapy with the compound of the present invention, preferred are an HIV reverse transcriptase inhibitor and an HIV protease inhibitor. Two or three, or even a greater number of medicaments can be used in combination, wherein a combination of medicaments having different action mechanisms is one of the preferable embodiments. In addition, selection of medicaments free of side effect duplication is preferable.

[0132]

Specific examples of the combination of medicaments include a combination of a group consisting of efavirenz, tenofovir, emtricitabine, indinavir, nelfinavir, atazanavir, ritonavir + indinavir, ritonavir + lopinavir, ritonavir + saquinavir, didanosine + lamivudine, zidovudine + didanosine, stavudine + didanosine, zidovudine + lamivudine, stavudine + lamivudine and tenofovir + emtricitabine, and the compound of

the present invention (Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. August 13, 2001). Particularly preferred is a combined use of two agents with efavirenz, indinavir, nelfinavir, tenofovir, emtricitabine, zidovudine or lamivudine, and a combined use of three agents with zidovudine + lamivudine, tenofovir + lamivudine, tenofovir + zidovudine, tenofovir + efavirenz, tenofovir + nelfinavir, tenofovir + indinavir, tenofovir + emtricitabine, emtricitabine + lamivudine, emtricitabine + zidovudine, emtricitabine + efavirenz, emtricitabine + nelfinavir, emtricitabine + indinavir, nelfinavir + lamivudine, nelfinavir + zidovudine, nelfinavir + efavirenz, nelfinavir + indinavir, efavirenz + lamivudine, efavirenz + zidovudine or efavirenz + indinavir.

[0133]

In the case of combined administration, the compound of the present invention can be administered simultaneously with a medicament to be used in combination (hereinafter concomitant drug) or administered at certain time intervals. In the case of combined administration, a pharmaceutical composition comprising the compound of the present invention and a concomitant drug can be administered. Alternatively, a pharmaceutical composition comprising the compound of the present invention and a pharmaceutical composition comprising a concomitant drug may be administered separately. The administration route of the compound of the present invention and that of the concomitant drug may be the same or different.

[0134]

In the case of a combined administration, the compound of the present invention can be administered once a day or several times a day in a single dose of 0.01 mg to 1 g, or may be administered at a smaller dose. The concomitant drug can be administered at a dose generally used for the prevention or treatment of an HIV infection, for example, at a single dose of 0.01 mg to 0.3 g. Alternatively, it may be administered in

a smaller dose.

[0135]

Now, production methods of the compound of the present invention are specifically explained. However, the present invention is not limited to these production methods. For production of the compound of the present invention, the order of reactions can be appropriately changed. The reactions may be performed from a reasonable step or a reasonable substitution moiety. In addition, an appropriate substituent conversion (conversion or further modification of substituent) step may be inserted between respective steps. When a reactive functional group is present, protection and deprotection may be appropriately performed. Furthermore, to promote the progress of reactions, reagents other than those exemplified below may be used as appropriate. The starting compounds whose production methods are not described are commercially available or can be easily prepared by a combination of known synthesis reactions. The compound obtained in each step can be purified by conventional methods such as distillation, recrystallization, column chromatography and the like. In some cases, the next step may be performed without isolation and purification.

In the following production methods, the "room temperature" means 1 to 40°C.

[0136]

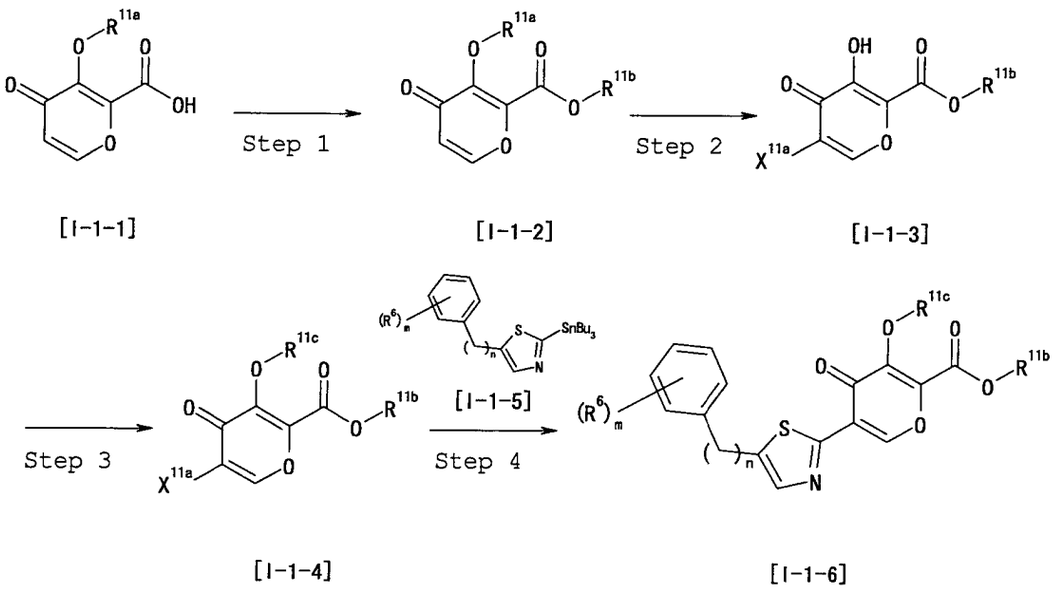
Production method I

[0137]

Production method I-1

Of compounds [I-3-1] in the below-mentioned production method I-3, compound [I-1-6] which is compound [I-3-1] wherein Y is CH can be synthesized by the following method.

[0138]



[I-1-1] [I-1-2] [I-1-3]

[I-1-4] [I-1-6]

[0139]

wherein R^{11a} and R^{11c} are the same or different and each is a hydroxyl-protecting group such as an acetyl group, a benzyl group, a methyl group, an ethyl group, an isopropyl group, a trimethylsilyl group, a triethylsilyl group, a tert-butyldimethylsilyl group, a triisopropylsilyl group, a tert-butyldiphenylsilyl group and the like, R^{11b} is a carboxyl-protecting group such as a methyl group, an ethyl group, a benzyl group, a tert-butyl group and the like, X^{11a} is a halogen atom such as a chlorine atom, a bromine atom and the like, and other symbols are each as described above.

[0140]

Step 1

Compound [I-1-2] can be obtained by introducing a protecting group into the carboxyl group of compound [I-1-1] according to a known method.

For example, when R^{11b} is a methyl group, compound [I-1-2] can be obtained by reacting compound [I-1-1] with trimethylsilyldiazomethane at a low temperature to room temperature in a single or mixed solvent such as tetrahydrofuran (THF), toluene, methanol, ethanol and the like.

[0141]

Step 2

Compound [I-1-3] can be obtained by introducing a halogen atom X^{11a} into compound [I-1-2] according to a known method.

For example, when X^{11a} is a bromine atom, compound [I-1-3] can be obtained by reacting compound [I-1-2] with a bromination reagent (e.g., bromine, trimethylphenylammonium tribromide etc.) at room temperature to under heating in a solvent such as chloroform, methylene chloride, acetic acid and the like.

[0142]

Step 3

Compound [I-1-4] can be obtained by introducing a protecting group into a hydroxyl group of compound [I-1-3] according to a known method.

For example, when R^{11c} is a benzyl group, compound [I-1-4] can be obtained by reacting compound [I-1-3] with benzyl halide (e.g., benzyl chloride, benzyl bromide etc.) at room temperature to under heating in the presence of a base such as potassium acetate, potassium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, potassium phosphate, triethylamine, sodium hydrogen phosphate, cesium carbonate, sodium hydride, potassium t-butoxide, lithiumdiisopropylamide (LDA) and the like in a solvent such as N,N-dimethylformamide (DMF), dimethylacetamide (DMA), acetonitrile, 1,2-dimethoxyethane, THF, toluene and the like.

[0143]

Step 4

Compound [I-1-6] can be obtained by subjecting compound [I-1-4] to a coupling reaction with compound [I-1-5] in the presence of a palladium catalyst (e.g., tris(dibenzylideneacetone)dipalladium(0), tetrakis(triphenylphosphine)palladium(0) and bis(triphenylphosphine)palladium(II) dichloride etc.) at room temperature to under heating in a solvent such as DMF, DMA, acetonitrile, toluene, 1,4-dioxane and the like. For preferable progress of the reaction, a ligand (e.g., tri(2-

furyl)phosphine, tributylphosphine etc.) may be further added.

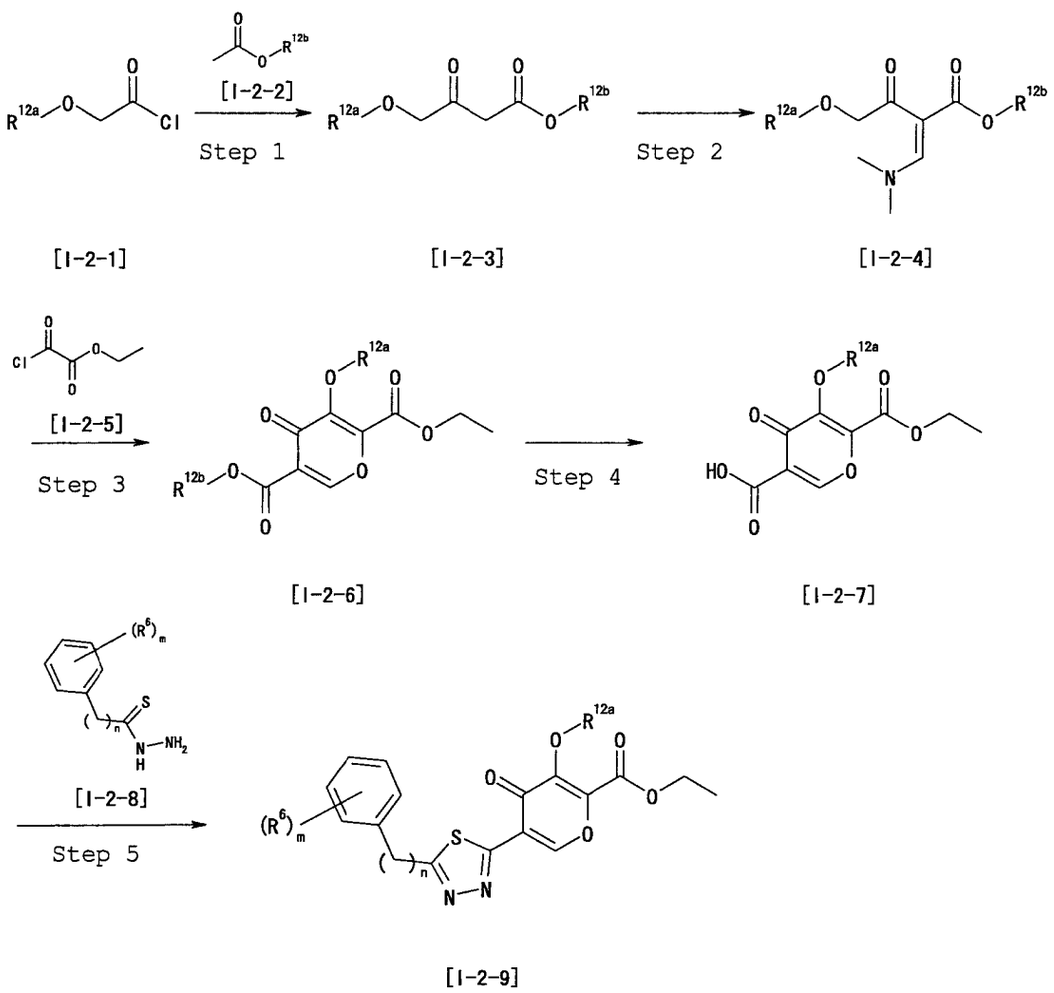
For example, compound [I-1-5] wherein n is 1 can be obtained in the same manner as in step 1R-2 and step 1R-3 of the below-mentioned Reference Example 1.

[0144]

Production method I-2

Of compounds [I-3-1] in the below-mentioned production method I-3, compound [I-2-9] which is compound [I-3-1] wherein Y is a nitrogen atom and R^{13b} is an ethyl group can be synthesized by the following method.

[0145]



[0146]

wherein R^{12a} is a hydroxyl-protecting group such as acetyl group, benzyl group, methyl group, ethyl group, isopropyl group, trimethylsilyl group, triethylsilyl group, tert-

butyldimethylsilyl group, triisopropylsilyl group, tert-butyldiphenylsilyl group and the like, R^{12b} is a carboxyl-protecting group such as methyl group, ethyl group, benzyl group, tert-butyl group and the like, and other symbols are each as described above.

[0147]

Step 1

Compound [I-2-3] can be obtained by reacting compound [I-2-1] with compound [I-2-2] at -78°C to room temperature conditions in a solvent such as DMF, DMA, dimethyl sulfoxide (DMSO), THF, toluene and the like, in the presence of a base such as sodium hydride, lithiumdiisopropylamide (LDA), lithium hexamethyldisilazide (LHMDS) and the like.

[0148]

Step 2

Compound [I-2-4] can be obtained by reacting Compound [I-2-3] with N,N-dimethylformamidedimethylacetal at room temperature to under heating in a solvent such as DMF, acetonitrile, THF, chloroform, ethyl acetate, methylene chloride, toluene and the like.

[0149]

Step 3

Compound [I-2-6] can be obtained by adding a base such as sodium hydride, LDA, LHMDS and the like to a solution of Compound [I-2-4] dissolved in a solvent such as DMF, DMA, DMSO, THF, toluene and the like at -78°C to room temperature, reacting the compound with compound [I-2-5] and treating same with triethylamine, diisopropylethylamine or the like.

[0150]

Step 4

Compound [I-2-7] can be obtained by removing the carboxyl-protecting group R^{12b} of compound [I-2-6] by a known method. For example, when the protecting group is a tert-butyl group, compound [I-2-7] can be obtained by stirring compound [I-2-6] at a low temperature to under heating in a single or

mixed solvent of hexane, chloroform, methylene chloride, ethyl acetate, toluene, 1,2-dimethoxyethane, 1,4-dioxane, THF, methanol, ethanol, 2-propanol, DMSO, DMF, DMA, acetonitrile, water and the like in the presence of acid such as p-toluenesulfonic acid, methanesulfonic acid, boron trifluoride, boron trichloride, boron tribromide, aluminum trichloride, hydrochloric acid, hydrogen bromide, phosphoric acid, sulfuric acid, acetic acid, trifluoroacetic acid and the like.

[0151]

Step 5

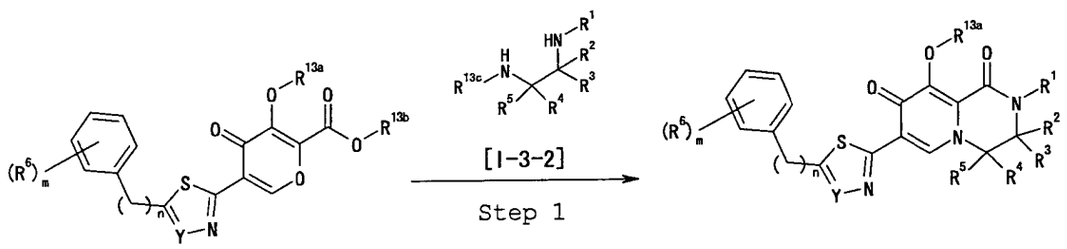
Compound [I-2-9] can be obtained by converting compound [I-2-7] to acid chloride by a known method, and further reacting the compound with compound [I-2-8]. Specifically, compound [I-2-9] can be obtained by converting compound [I-2-7] to acid chloride with a chlorinating agent such as oxalyl chloride, thionyl chloride, phosphorus trichloride and the like at a low temperature to room temperature in a single or mixed solvent of hexane, chloroform, methylene chloride, ethyl acetate, toluene, 1,2-dimethoxyethane, 1,4-dioxane, THF and the like in the presence of a catalytic amount of DMF where necessary, and reacting the compound with compound [I-2-8].

[0152]

production method I-3

A compound represented by the above-mentioned formula [I] can be synthesized by the following method.

[0153]

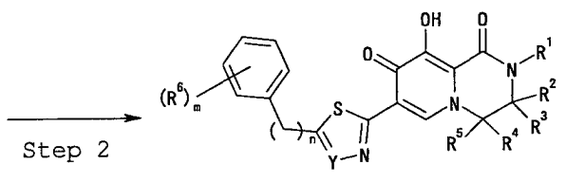


[I-3-1]

[I-3-2]

Step 1

[I-3-3]



Step 2

[I]

[0154]

wherein R^{13a} is a hydroxyl-protecting group such as acetyl group, benzyl group, methyl group, ethyl group, isopropyl group, trimethylsilyl group, triethylsilyl group, tert-butyldimethylsilyl group, triisopropylsilyl group, tert-butyldiphenylsilyl group and the like, R^{13b} is a carboxyl-protecting group such as methyl group, ethyl group, benzyl group, tert-butyl group and the like, R^{13c} is an amino-protecting group such as benzyloxycarbonyl group, tert-butoxycarbonyl group, benzyl group and the like, and other symbols are each as described above.

[0155]

Step 1

Compound [I-3-3] can be obtained by reacting compound [I-3-1] with compound [I-3-2], wherein amino-protecting group R^{13c} is removed in advance according to a known method at room temperature to under heating in a single or mixed solvent of chloroform, dichloromethane, DMF, DMA, DMSO, acetonitrile, 1,2-dimethoxyethane, THF, toluene, water and the like, and cyclizing the compound in the presence of a base such as triethylamine, diisopropylamine, diisopropylethylamine, diazabicycloundecene, sodium carbonate, potassium carbonate,

sodium hydrogen carbonate and the like. The cyclization reaction can also be performed in the presence of acid such as acetic acid, p-toluenesulfonic acid, methanesulfonic acid, boron trifluoride, boron trichloride, boron tribromide, hydrochloric acid, hydrogen bromide, phosphoric acid, sulfuric acid and the like.

[0156]

Step 2

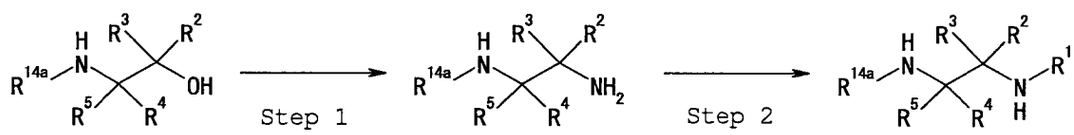
Compound [I] can be obtained by removing the hydroxyl-protecting group R^{13a} of compound [I-3-3] by a known method. For example, when the protecting group is a benzyl group, compound [I] can be obtained by stirring compound [I-3-3] at a low temperature to room temperature in a single or mixed solvent of hexane, chloroform, methylene chloride, ethyl acetate, toluene, methanol, ethanol, 2-propanol, THF, 1,4-dioxane, acetonitrile, water and the like, in the presence of acid such as hydrochloric acid, sulfuric acid, hydrogen bromide, phosphoric acid, acetic acid, trifluoroacetic acid and the like. The acid may be used as a solvent.

[0157]

Production method I-4

Compound [I-3-2] in the above-mentioned production method I-3 (corresponding to the following compound [I-4-3]) can be synthesized by the following method.

[0158]



[I-4-1] [I-4-2] [I-4-3]

[0159]

wherein R^{14a} is an amino-protecting group such as benzyloxycarbonyl group, tert-butoxycarbonyl group, benzyl group and the like, and other symbols are each as described above.

[0160]

Step 1

Compound [I-4-1] obtainable from a commercially available compound by a known method is reacted with phthalimide at a low temperature to under heating in a single or mixed solvent of THF, methylene chloride, chloroform, DMF, ethyl acetate, toluene and the like in the presence of a phosphorus reagent such as triphenylphosphine, diphenyl(2-pyridyl)phosphine, tributylphosphine, tri-tert-butylphosphine and the like and an azo compound such as diisopropylazodicarboxylate, diethylazodicarboxylate, N,N,N',N'-tetramethylazodicarboxamide, 1,1'-(azodicarbonyl)dipiperidine and the like, and the obtained compound is further treated with hydrazine to remove a phthaloyl group to give amine compound [I-4-2].

[0161]

Step 2

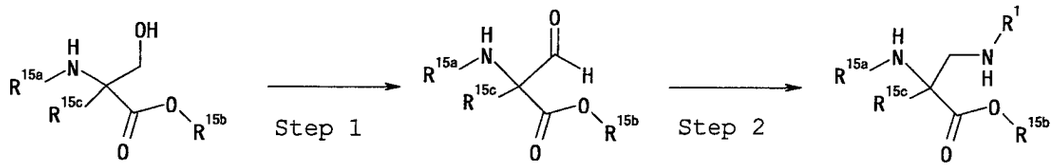
Compound [I-4-2] is reacted with a ketone compound or aldehyde compound at a low temperature to room temperature in a solvent such as DMF, acetonitrile, THF, chloroform, ethyl acetate, methylene chloride, toluene and the like, and the mixture is stirred in the presence of a reducing agent such as sodium borohydride, sodium triacetoxyborohydride and the like to introduce substituent R^1 into the amino group of compound [I-4-2], whereby compound [I-4-3] can be obtained.

[0162]

Production method I-5

Of compounds [I-3-2] in the above production method I-3, a compound, which is compound [I-3-2] wherein particularly R^2 and R^3 are each a hydrogen atom, one of R^4 and R^5 is a carboxyl group or $-CO-NR^aR^b$ wherein R^a and R^b are as described above, and the other is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the aforementioned group A, can be synthesized by the following method.

[0163]



[I-5-1] [I-5-2] [I-5-3]

[0164]

wherein R^{15a} is an amino-protecting group such as benzyloxycarbonyl group, tert-butoxycarbonyl group, benzyl group and the like, R^{15b} is a carboxyl-protecting group such as methyl group, ethyl group, benzyl group, tert-butyl group and the like, R^{15c} is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the aforementioned group A, and other symbols are each as described above.

[0165]

Step 1

Compound [I-5-2] can be obtained by oxidizing the hydroxyl group of compound [I-5-1] obtainable from a commercially available compound by a known method, to a aldehyde group by a chromium oxide-pyridine complex (e.g., pyridinium chlorochromate, pyridinium dichromate and the like), a metal oxidant (e.g., chromium oxide, silver carbonate, manganese dioxide and the like), by DMSO oxidization using various DMSO activators such as oxalyl chloride, trifluoroacetic anhydride, acetic anhydride, dicyclohexylcarbodiimide (DCC), sulfur trioxide-pyridine complex and the like, Dess-Martin oxidization and the like according to a known method.

[0166]

Step 2

Compound [I-5-3] can be obtained by subjecting the aldehyde group of compound [I-5-2] to a reductive amination under similar conditions as in production method I-4, step 2. The obtained compound [I-5-3] is cyclized by the above-mentioned method, and the carboxyl-protecting group R^{15b} is

removed by a known method and, where necessary, the resulting compound is reacted with an amine compound by a known method to give the object compound.

[0167]

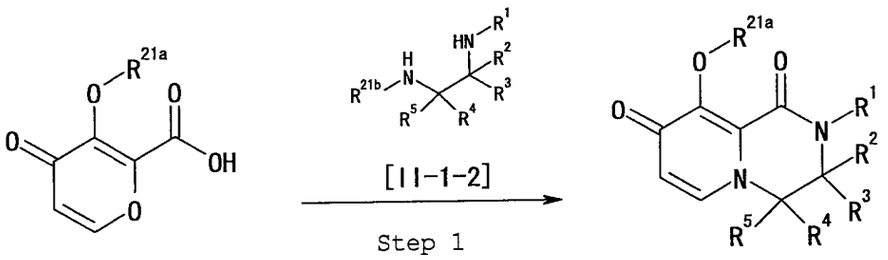
Production method II

[0168]

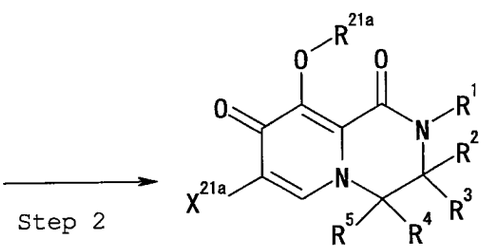
Production method II-1

Of the compounds represented by the above-mentioned formula [I], compound [II-1-6], which is compound [I] wherein Y is CH can be synthesized by the following method.

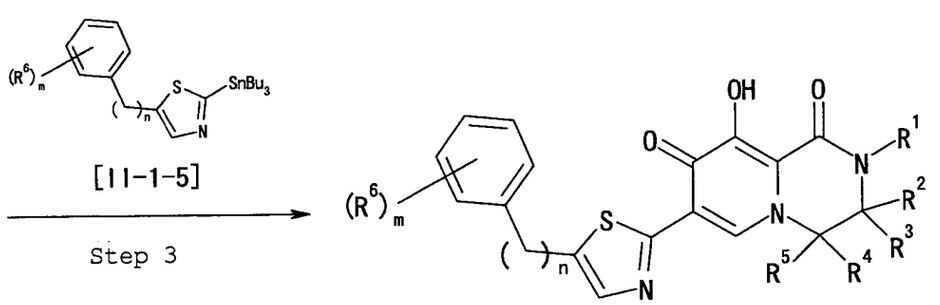
[0169]



[II-1-1] [II-1-3]



[II-1-4]



[II-1-6]

[0170]

wherein R^{21a} is a hydroxyl-protecting group such as acetyl group, benzyl group, methyl group, ethyl group, isopropyl group, trimethylsilyl group, triethylsilyl group, tert-butyldimethylsilyl group, triisopropylsilyl group, tert-butyldiphenylsilyl group and the like, R^{21b} is an amino-protecting group such as benzyloxycarbonyl group, tert-butoxycarbonyl group, benzyl group and the like, X^{21a} is a leaving group such as a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom, iodine atom and the like), p-toluenesulfonyloxy group (OTs), methanesulfonyloxy group (OMs), trifluoromethanesulfonyloxy group (OTf) and the like, and other symbols are each as described above.

[0171]

Step 1

Compound [II-1-3] can be obtained by converting compound [II-1-1] to acid chloride by a known method at a low temperature to under heating, reacting the acid chloride with compound [II-1-2], removing the amino-protecting group R^{21b}, and stirring the mixture in the presence of a base such as potassium acetate, potassium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, potassium phosphate, triethylamine, diisopropylethylamine, sodium hydrogen phosphate, cesium carbonate and the like.

Compound [II-1-2] can be obtained by a method similar to that of Production method I-4.

[0172]

Step 2

Compound [II-1-4] can be obtained by introducing leaving group X^{21a} into compound [II-1-3] by a known method.

For example, when the leaving group X^{21a} is a bromine atom, the bromine atom is introduced into compound [II-1-3] by a method similar to that in production method I-1, step 2 to give compound [II-1-4].

[0173]

Step 3

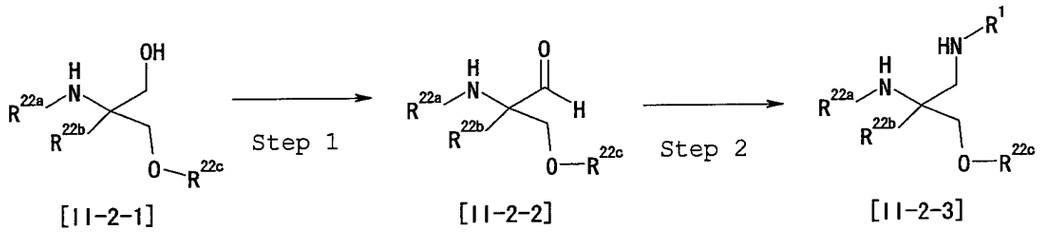
Compound [II-1-4] is reacted with compound [II-1-5] by a method similar to that of production method I-1, step 4, and the hydroxyl-protecting group R^{21a} is removed by a method similar to that of production method I-3, step 2, whereby compound [II-1-6] can be obtained.

[0174]

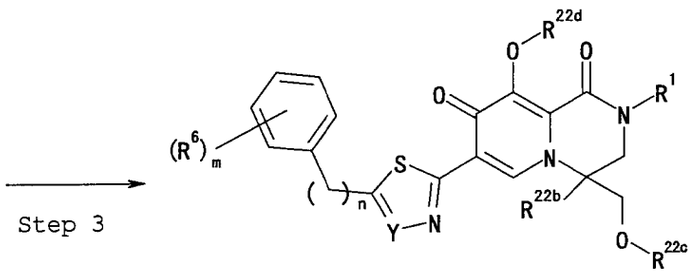
Production method II-2

Of the compounds represented by the above-mentioned formula [I], a compound, which is compound [I] wherein particularly R^2 and R^3 are each a hydrogen atom, and one of R^4 and R^5 is a methyl group substituted by $-NR^{A3}R^{A4}$ wherein R^{A3} and ^{A4} are as described above, and the other is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the aforementioned group A, can be synthesized by the following method.

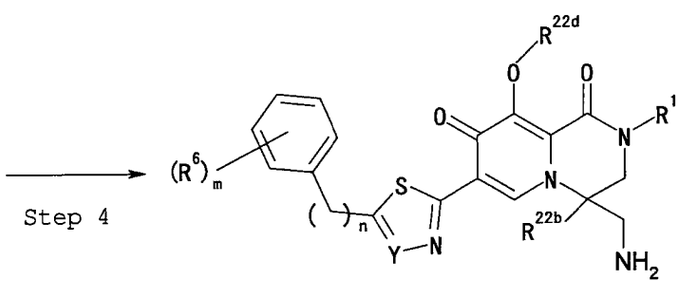
[0175]



[II-2-1] [II-2-2] [II-2-3]



[II-2-4]



[II-2-5]

[0176]

wherein R^{22a} is an amino-protecting group such as benzyloxycarbonyl group, tert-butoxycarbonyl group, benzyl group and the like, R^{22b} is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the aforementioned group A, R^{22c} and R^{22d} are the same or different, and each is a hydroxyl-protecting group such as acetyl group, benzyl group, methyl group, ethyl group, isopropyl group, trimethylsilyl group, triethylsilyl group, tert-butyldimethylsilyl group, triisopropylsilyl group, tert-butyldiphenylsilyl group and the like, and other symbols are each as described above.

[0177]

Step 1

The hydroxyl group of compound [II-2-1] is oxidized, by a

known method to give aldehyde group, whereby compound [II-2-2] can be obtained. The known method is the same as the one indicated for, for example, the production method I-5, step 1.

[0178]

Step 2

Compound [II-2-3] can be obtained by subjecting compound [II-2-2] to reductive amination by the same method as in the production method I-5, step 2.

[0179]

Step 3

Compound [II-2-4] can be obtained from compound [II-2-3] by the same method as in production method II-1, step 1 to step 3.

[0180]

Step 4

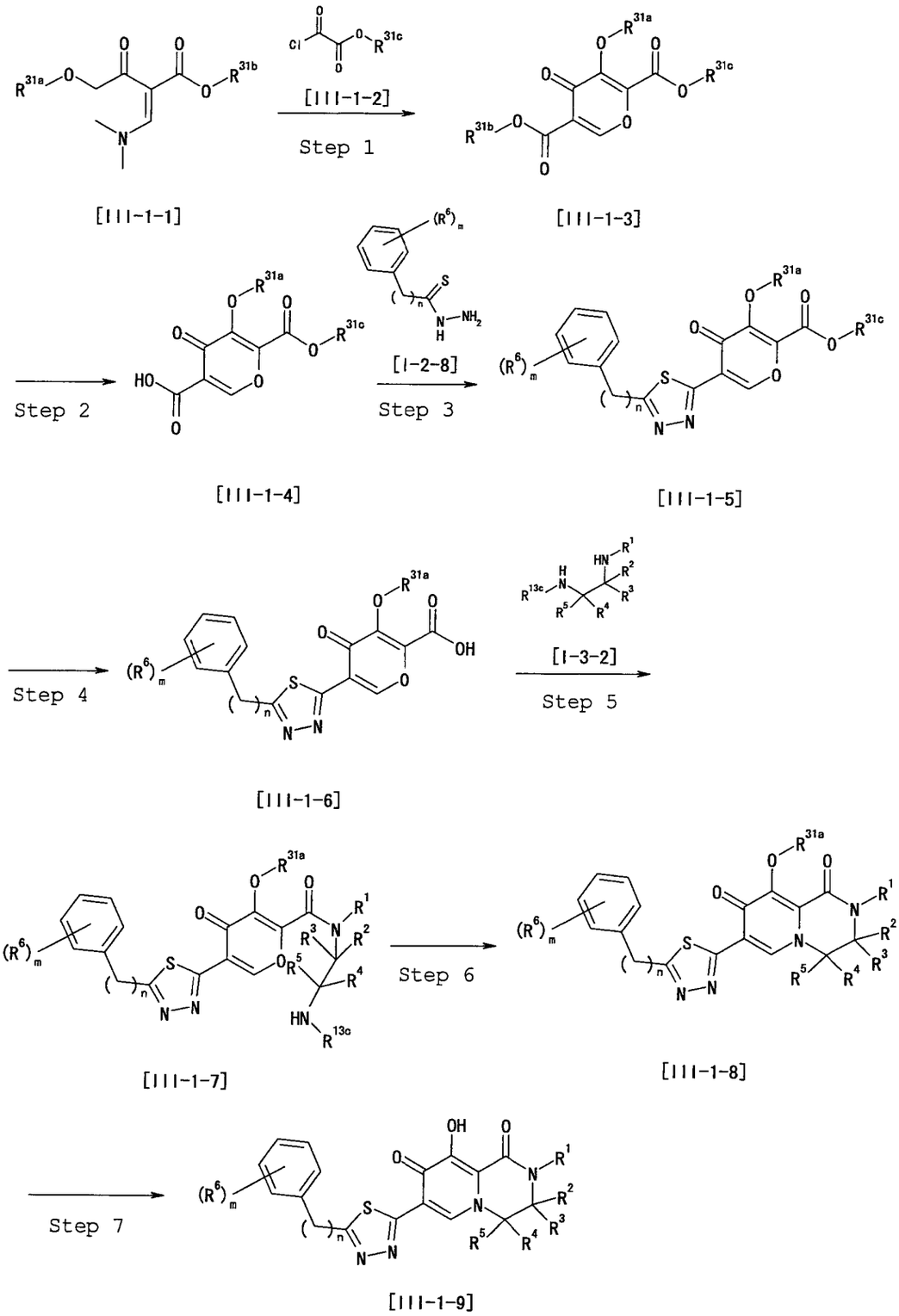
The hydroxyl-protecting group R^{22c} of compound [II-2-4] is removed by a known method, and the hydroxyl group is appropriately subjected to substituent conversion to a leaving group (OTs, OMs, OTf etc.). After reaction with potassium phthalimide, and the phthaloyl group is removed by a method similar to production method I-4, step 1 to give compound [II-2-5]. The obtained compound [II-2-5] is subjected to an appropriately combination of removal of hydroxyl-protecting group R^{22d} by a method similar to production method I-3, step 2, and modification of amino group of compound [II-2-5] by a known method to give the object compound.

[0181]

Production method III

Of compounds represented by the above-mentioned formula [I], compound [III-1-9], which is compound [I] wherein Y is a nitrogen atom can be synthesized by the following method.

[0182]



[0183]

wherein R^{31a} is a hydroxyl-protecting group such as acetyl group, benzyl group, methyl group, ethyl group, isopropyl group, trimethylsilyl group, triethylsilyl group, tert-butyldimethylsilyl group, triisopropylsilyl group, tert-

butyldiphenylsilyl group and the like, R^{31b} and R^{31c} are the same or different and each is a carboxyl-protecting group such as methyl group, ethyl group, benzyl group, tert-butyl group and the like, and other symbols are each as described above.

[0184]

Step 1

Compound [III-1-3] can be obtained by reacting compound [III-1-1] with compound [III-1-2] by a method similar to production method I-2, step 3.

[0185]

Step 2

Compound [III-1-4] can be obtained by removing the carboxyl-protecting group R^{31b} of compound [III-1-3] by a method similar to production method I-2, step 4.

[0186]

Step 3

Compound [III-1-5] can be obtained by reacting compound [III-1-4] with compound [I-2-8] by a method similar to production method I-2, step 5.

[0187]

Step 4

Compound [III-1-6] can be obtained by removing the carboxyl-protecting group R^{31c} of compound [III-1-5] by a known method.

[0188]

Step 5

Compound [III-1-7] can be obtained by converting compound [III-1-6] to acid chloride by a method similar to production method I-2, step 5, and reacting the acid chloride with compound [I-3-2] in a solvent such as hexane, chloroform, methylene chloride, ethyl acetate, toluene, 1,2-dimethoxyethane, 1,4-dioxane, THF and the like in the presence of a base such as potassium acetate, potassium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, potassium phosphate, triethylamine, diisopropylethylamine,

sodium hydrogen phosphate, cesium carbonate and the like.

[0189]

Step 6

Compound [III-1-8] can be obtained by removing the amino-protecting group R^{13c} of compound [III-1-7] by a known method, and performing cyclization by a method similar to a cyclization reaction of production method II-1, step 1 in the presence of a base.

[0190]

Step 7

Compound [III-1-9] can be obtained by removing the hydroxyl-protecting group R^{31a} of compound [III-1-8] by a known method. For example, when the protecting group is a benzyl group, a method similar to production method I-3, step 2 can be used.

Examples

[0191]

Now, the production methods of the compound of the present invention are specifically explained by referring to Examples, which are not to be construed as limitative.

The abbreviations used in the Examples mean the following.

Bn: benzyl group

Boc: tert-butoxycarbonyl group

Et: ethyl group

Me: methyl group

Ms: methanesulfonyl group

TBS: tert-butyldimethylsilyl group

TFA: trifluoroacetic acid

THP: tetrahydropyranyl group

Z: benzyloxycarbonyl group

In addition, the following ^{1}H-NMR values were measured by resolution 400 MHz.

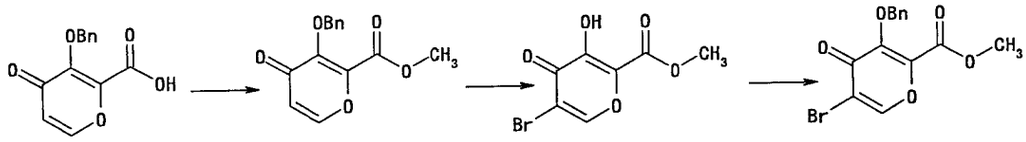
[0192]

Reference Example 1

[0193]

step 1R-1

[0194]



[0195]

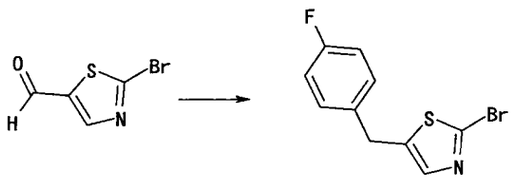
3-benzyloxy-4-oxo-4H-pyran-2-carboxylic acid (11.43 g) was suspended in methanol (20 mL)-tetrahydrofuran (80 mL), 2M (trimethylsilyl)diazomethane/hexane solution (46.4 mL) was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 1.5 hr. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in chloroform (80 mL). Thereto was added bromine (23 mL) and the mixture was stirred for 2 days at 75°C. The mixture was allowed to cool to room temperature, hexane was added and the precipitated solid was collected by filtration. The obtained solid was dissolved in dimethylformamide (54 mL), potassium carbonate (7.1 g) and benzyl bromide (5.6 mL) were added, and the mixture was stirred at 80°C for 40 min. The mixture was allowed to cool to room temperature and filtered. The filtrate was concentrated and 1N aqueous hydrochloric acid solution was added to the obtained residue. The mixture was extracted twice with ethyl acetate. The combined ethyl acetate layer was washed with saturated brine, dried, and concentrated. The concentrate was purified by silica gel column chromatography (ethyl acetate:hexane=1:20 - 1:4), the eluate was concentrated, and the precipitated crystals were collected by filtration to give the object compound (7.65 g) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 8.11 (s, 1H), 7.49-7.44 (m, 2H), 7.40-7.32 (m, 3H), 5.32 (s, 2H), 3.89 (s, 3H).

[0196]

step 1R-2

[0197]



[0198]

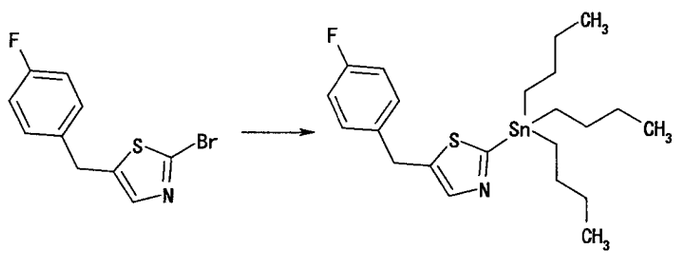
To a solution of 2-bromothiazole-5-carbaldehyde (14 g) in THF (300 mL) was added dropwise 1M (4-fluorophenyl)magnesium bromide/THF solution (80 mL) at -78°C, and the mixture was stirred for 1 hr. Saturated aqueous ammonium chloride solution was added, and the mixture was allowed to cool to room temperature, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried, and concentrated. Trifluoroacetic acid (100 mL) and triethylsilane (58 mL) were added to the obtained residue, and the mixture was stirred for 100 min at 75°C. The mixture was allowed to cool to room temperature and concentrated, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:50 - 1:9) to give the object compound (16.8 g) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 7.31-7.29 (m, 1H), 7.21-7.14 (m, 2H), 7.05-6.98 (m, 2H), 4.07 (s, 2H).

[0199]

step 1R-3

[0200]



[0201]

To a solution of the compound (3.2 g) obtained in step 1R-2 in THF (50 mL) was added dropwise 1.6M n-butyllithium/hexane solution (8.1 mL) at -78°C and the mixture was stirred for 10 min. Tributyltin chloride (3.5 mL) was added, and the mixture was stirred at -78°C for 30 min and at

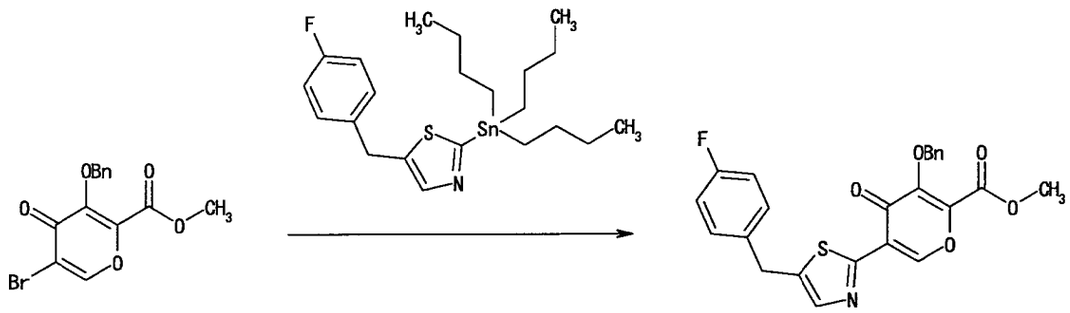
room temperature for 30 min. Ice-cold water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried, and concentrated to give the object compound (6.2 g) described in the above-mentioned scheme as a crude product.

^{1}H-NMR (THF) δ: 7.76-7.74 (m, 1H), 7.25-7.21 (m, 2H), 7.03-6.97 (m, 2H), 4.19 (s, 2H), 1.65-1.56 (m, 6H), 1.40-1.28 (m, 6H), 1.20-1.13 (m, 6H), 0.91-0.85 (m, 9H).

[0202]

step 1R-4

[0203]



[0204]

Under an argon stream, tris(dibenzylideneacetone)dipalladium(0) (84 mg) and tri(2-furyl)phosphine (85 mg) were suspended in toluene (1.5 mL), and the suspension was stirred at room temperature for 15 min. The compound (890 mg) obtained in step 1R-3 and the compound (310 mg) obtained in step 1R-1 were added, and the mixture was stirred at 80°C for 1 hr. The obtained reaction mixture was filtered through celite, and concentrated, and the concentrate was purified by silica gel column chromatography (ethyl acetate:hexane=1:20 - 1:4) to give the object compound (190 mg) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 8.91 (s, 1H), 7.62-7.61 (m, 1H), 7.51-7.45 (m, 2H), 7.40-7.32 (m, 3H), 7.25-7.19 (m, 2H), 7.04-6.97 (m, 2H), 5.37 (s, 2H), 4.19 (s, 2H), 3.91
(s, 3H).

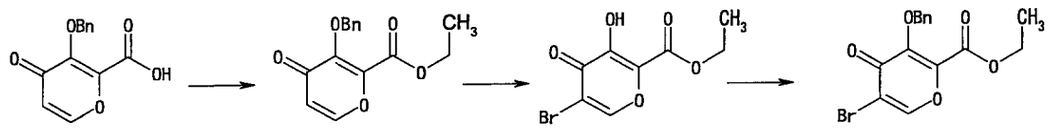
[0205]

Reference Example 2

[0206]

step 2R-1

[0207]



[0208]

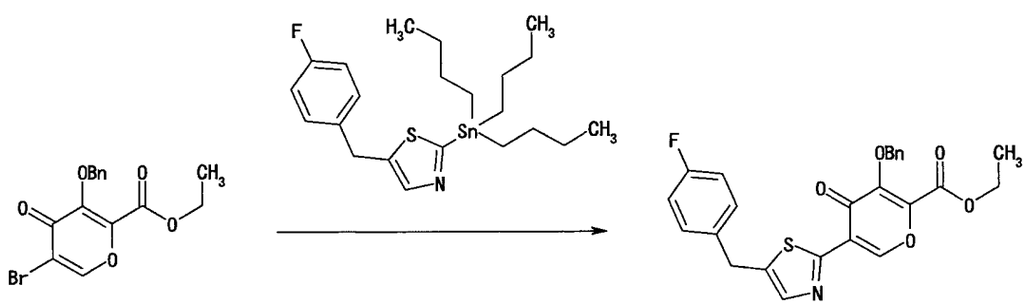
In the same manner as in step 1R-1 except that 3-benzyloxy-4-oxo-4H-pyran-2-carboxylic acid (15.0 g) was ethylated with iodoethane, the object compound (10.97 g) described in the above-mentioned scheme was obtained.

^{1}H-NMR ($CDCl_3$) δ: 8.11 (s, 1H), 7.50-7.46 (m, 2H), 7.40-7.32 (m, 3H), 5.31 (s, 2H), 4.36 (q, 2H, J = 7.2 Hz), 1.33 (t, 3H, J = 7.2 Hz).

[0209]

step 2R-2

[0210]



[0211]

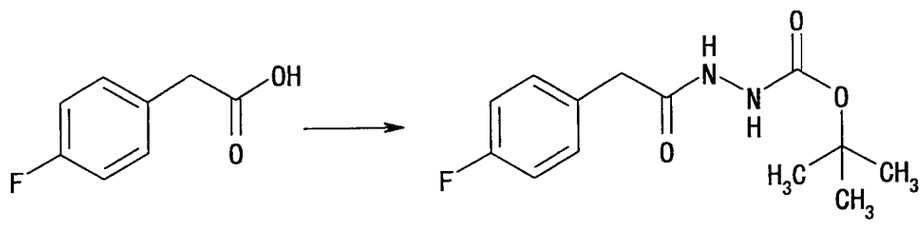
In the same manner as in step 1R-4, the object compound (1.0 g) described in the above-mentioned scheme was obtained from the compound (1.2 g) obtained in step 2R-1.

^{1}H-NMR ($CDCl_3$) δ: 8.91 (s, 1H), 7.62-7.61 (m, 1H), 7.51-7.47 (m, 2H), 7.39-7.31 (m, 3H), 7.25-7.20 (m, 2H), 7.04-6.97 (m, 2H), 5.37 (s, 2H), 4.38 (q, 2H, J = 7.2 Hz), 4.19 (s, 2H), 1.34 (t, 3H, J = 7.2 Hz).

[0212]

Reference Example 3

[0213]



[0214]

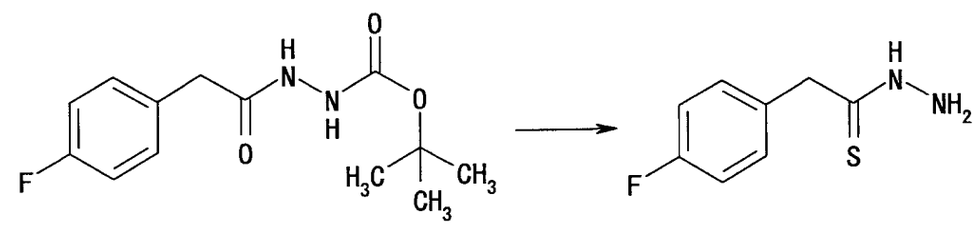
step 3R-1

To a solution of 4-fluorophenylacetic acid (25 g) and tert-butyl carbazate (22.5 g) in DMF (200 mL) were added 1-hydroxybenzotriazole hydrate (HOBT·H_2O (27.3 g)) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl (34.1 g)), and the mixture was stirred at room temperature overnight. Saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was stirred for a while and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated to give the object compound (32.3 g) described in the above-mentioned scheme as a crude product.

[0215]

step 3R-2

[0216]



[0217]

To a solution of the compound (32.3 g) obtained in step 3R-1 in THF (300 mL) was added a Lawesson reagent (48.7 g), and the mixture was stirred at 50°C overnight and allowed to cool. The reaction mixture was poured into a stirred saturated aqueous sodium hydrogen carbonate solution by small portions, and the mixture was stirred at room temperature for 30 min.

The mixture was extracted twice with ethyl acetate, and the organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated. To the residue was added 4N hydrochloric acid/dioxane solution (300 mL), and the mixture was stirred at room temperature for 1 hr. The precipitated salt was collected by filtration, and dissolved in water (200 mL), and the solution was neutralized with sodium hydrogen carbonate and extracted twice with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate, and concentrated. To the residue was added ethyl acetate/hexane (1:4) solution and the mixture was slurry washed. The residue was collected by filtration, and dried to give the object compound (15.78 g) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 8.27-8.03 (br m, 1H), 7.26-7.20 (m, 2H), 7.10-7.03 (m, 2H), 4.88-4.75 (br m, 2H), 4.08 (s, 2H).

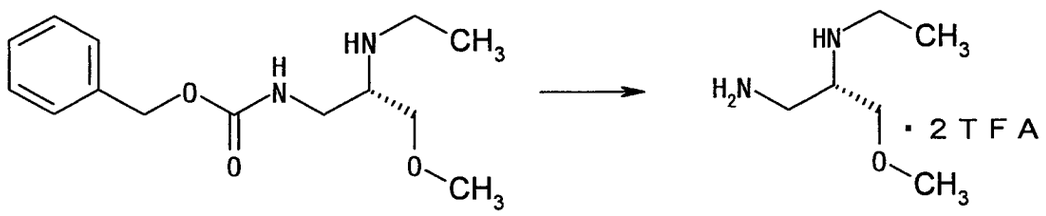
[0218]

Example 1

[0219]

step 1-1

[0220]



[0221]

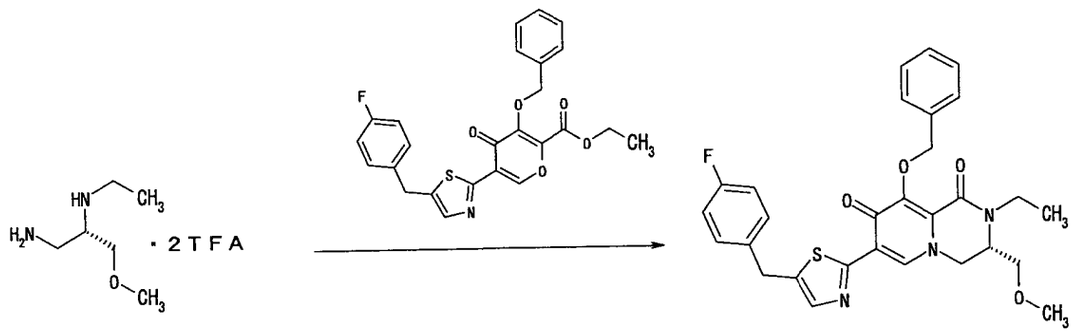
To a solution of (S)-2-ethylamino-3-methoxypropylcarbamic acid benzyl ester (76 mg) in methanol (10 mL) was added a 7.5% palladium-carbon catalyst (100 mg), and the reaction mixture was stirred under a moderate-pressure (0.4 MPa) in a hydrogen atmosphere at room temperature for 3 hr. The reaction mixture was filtered through celite, trifluoroacetic acid (1 mL) was added and the mixture was concentrated to give the object

compound (133 mg) described in the above-mentioned scheme as a crude product.

[0222]

step 1-2

[0223]



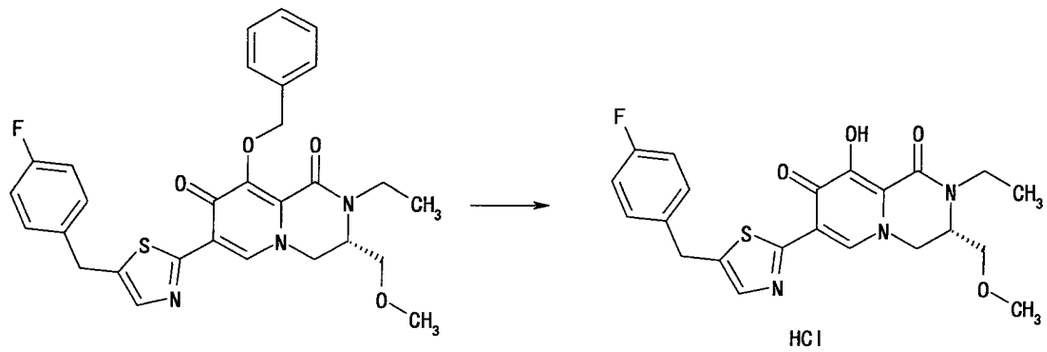
[0224]

To a solution of the compound (55 mg) obtained in step 1-1 in tetrahydrofuran (1.5 mL) was added diisopropylethylamine (160 μL), and the mixture was stirred for 10 min. A solution of the compound (46 mg) obtained in Reference Example 2 in tetrahydrofuran (1 mL) was added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated, toluene (4 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (200 μL) were added, and the mixture was stirred at 110°C for 15 min. Acetic acid (500 μL) was added, and the mixture was stirred at 110°C for 1 hr. The reaction mixture was allowed to cool to room temperature, and diluted with ethyl acetate. The mixture was washed with 5% aqueous potassium hydrogen sulfate solution, dried and concentrated, and the concentrate was purified by silica gel thin layer chromatography (ethyl acetate:methanol=20:1) to give the object compound (56 mg) described in the above-mentioned scheme.

[0225]

step 1-3

[0226]



[0227]

Compound (56 mg) obtained in step 1-2 was dissolved in trifluoroacetic acid (1.0 mL), and the mixture was stood at room temperature for 1 hr. The reaction solution was concentrated, ethyl acetate was added and the mixture was concentrated. Ethyl acetate, 4N hydrochloric acid/ethyl acetate solution, and hexane were added to allow crystallization to give the object compound (28 mg) described in the above-mentioned scheme.

^{1}H-NMR (DMSO-d_6) δ: 12.30 (br s, 1H), 8.64 (s, 1H), 7.66 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.57 (d, 1H, J=13.5 Hz), 4.39 (dd, 1H, J=13.5, 3.9 Hz), 4.19 (s, 2H), 4.12-4.10 (m 1H), 3.87-3.80 (m, 1H), 3.53-3.44 (m, 2H), 3.27-3.22 (m, 1H), 3.20 (s, 3H), 1.18 (t, 3H, J=7.1 Hz).

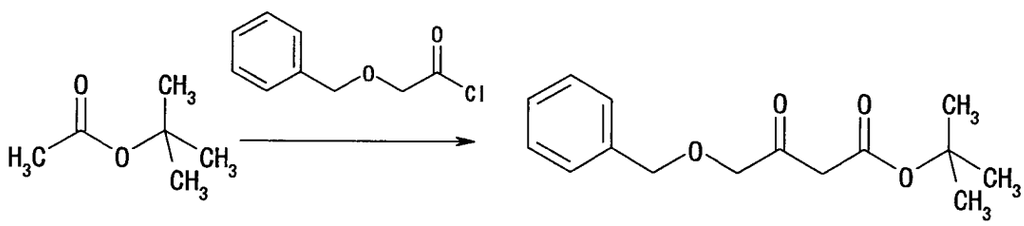
[0228]

Example 2

[0229]

step 2-1

[0230]



[0231]

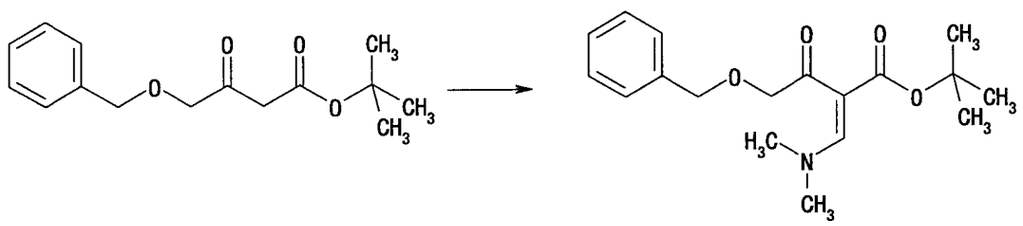
Under nitrogen, a solution of 1M lithium bis(trimethylsilyl)amide-THF/ethylbenzene (100 mL) in THF (100 mL) was cooled to -70°C, and tert-butyl acetate (13.5 mL) was

added dropwise under stirring. After stirring for 15 min, benzyloxyacetyl chloride (7.52 mL) was added dropwise. After stirring for 1 hr, 2N aqueous hydrochloric acid solution was added to the reaction mixture until its pH reached 3 and the mixture was allowed to warm to room temperature. The mixture was extracted with ethyl acetate, and the organic layer was washed with 2N aqueous hydrochloric acid solution and saturated brine, dried over sodium sulfate and concentrated. The above operation was repeated, and the both were combined to give the object compound (40.3 g) described in the above-mentioned scheme as a crude product.

[0232]

step 2-2

[0233]



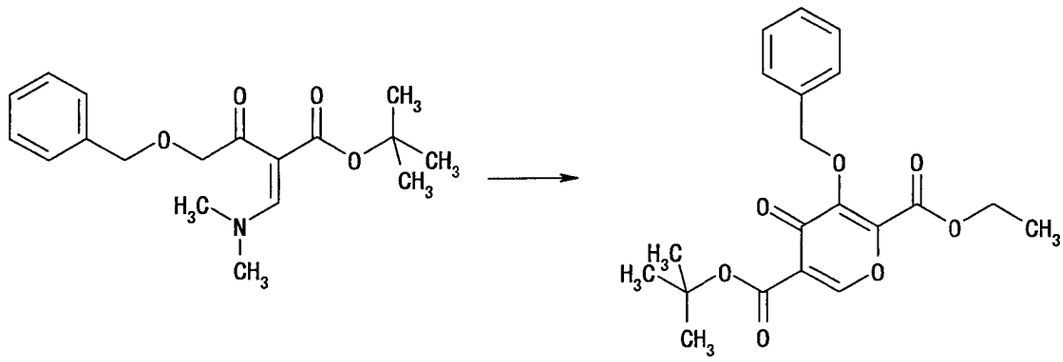
[0234]

To a solution of the compound (38 g) obtained in step 2-1 in toluene (80 mL) was added dimethylformamidedimethylacetal (38 mL), and the mixture was stirred at 100°C for 1 hr. The mixture was allowed to cool, and concentrated, and the concentrate was purified by silica gel column chromatography (ethyl acetate:hexane=1:2 - ethyl acetate) to give the object compound (11.3 g) described in the above-mentioned scheme. ^{1}H-NMR ($CDCl_3$) δ: 7.66 (s, 1H), 7.40-7.13 (m, 5H), 4.60 (s, 2H), 4.42 (s, 2H), 3.40-2.65 (m, 6H), 1.45 (s, 9H).

[0235]

step 2-3

[0236]



[0237]

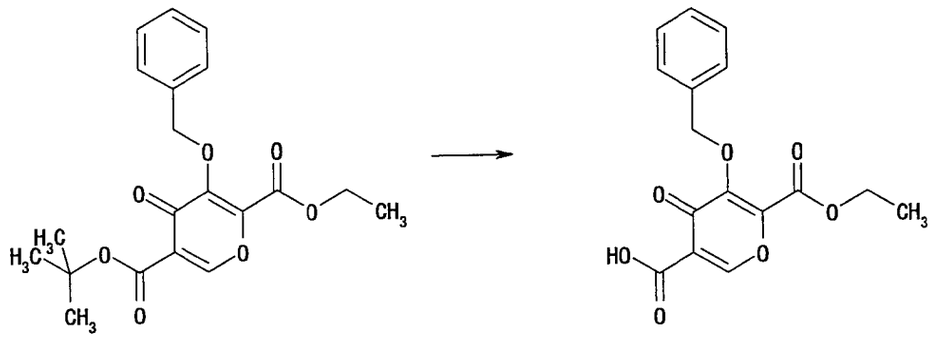
Under nitrogen, a solution of 1M lithium bis(trimethylsilyl)amide-THF/ethylbenzene (42.5 mL) in THF (150 mL) was cooled to -70°C, and a solution of the compound (11.3 g) obtained in step 2-2 in THF (50 mL) was added dropwise over 3 min under stirring. After stirring for 20 min, ethyl chloroglyoxylate (4.75 mL) was added at once. After stirring for 25 min, saturated aqueous potassium hydrogen sulfate solution and ethyl acetate were added and the mixture was allowed to warm to room temperature. The organic layer was separated, washed with saturated brine, dried over sodium sulfate, and concentrated. Toluene was added to the residue, and the mixture was concentrated once. Toluene (100 mL) and triethylamine (10 mL) were added and the mixture was stirred at room temperature. One hour later, the mixture was concentrated, and the concentrate was purified by silica gel column chromatography (ethyl acetate:hexane=1:6 - 1:3) to give the object compound (6.03 g) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 8.39 (s, 1H), 7.51-7.47 (m, 2H), 7.39-7.30 (m, 3H), 5.32 (s, 2H), 4.34 (q, 2H, J = 7.2 Hz), 1.57 (s, 9H), 1.31 (t, 3H, J = 7.2 Hz).

[0238]

step 2-4

[0239]



[0240]

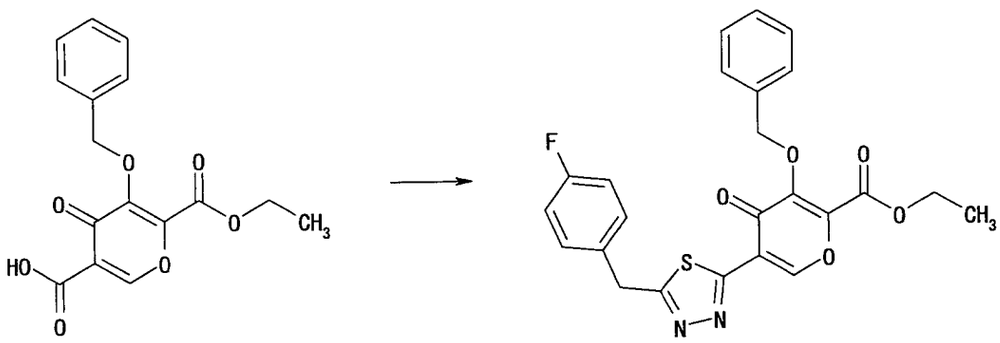
To a solution of the compound (18.7 g) obtained in step 2-3 in ethyl acetate (20 mL) was added 4N hydrochloric acid/ethyl acetate (200 mL) under stirring, and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added hexane (1 L), the mixture was stirred for a while, and the crystals were collected by filtration, and dried to give the object compound (11.1 g) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 13.03 (s, 1H), 8.80 (s, 1H), 7.47-7.43 (m, 2H), 7.41-7.35 (m, 3H), 5.38 (s, 2H), 4.40 (q, 2H, J = 7.2 Hz), 1.35 (t, 3H, J = 7.2 Hz).

[0241]

step 2-5

[0242]



[0243]

To a solution of the compound (6 g) obtained in step 2-4 in toluene (80 mL) were added oxalyl chloride (3.27 mL) and dimethylformamide (0.04 mL) under stirring, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated, chloroform (100 ml) and the compound (5.22

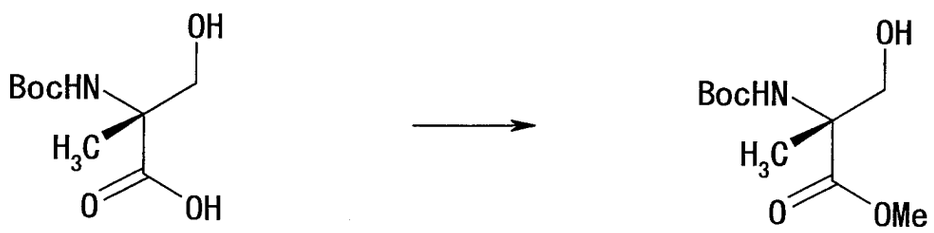
g) obtained in Reference Example 3 were added, and the mixture was stirred at room temperature overnight. 5% Aqueous potassium hydrogen sulfate solution was added, and the mixture was extracted twice with chloroform. The organic layer was washed with 5% aqueous potassium hydrogen sulfate solution and saturated brine, dried over magnesium sulfate, and concentrated. The concentrate was purified by silica gel column chromatography (ethyl acetate:hexane=1:4 - 1:3), ethyl acetate/hexane (1:3) solution was added, and the mixture was slurry washed. The residue was collected by filtration, and dried to give the object compound (6.348 g) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 9.07 (s, 1H), 7.49-7.44 (m, 2H), 7.39-7.28 (m, 5H), 7.07-7.00 (m, 2H), 5.35 (s, 2H), 4.46 (s, 2H), 4.39 (q, 2H, J = 7.1 Hz), 1.34 (t, 3H, J = 7.1 Hz).

[0244]

step 2-6

[0245]



[0246]

To a solution of (R)-2-tert-butoxycarbonylamino-3-hydroxy-2-methylpropionic acid (5.00 g) in dimethylformamide (50 mL) were added potassium carbonate (6.31 g) and iodomethane (2.84 mL), and the mixture was stirred at room temperature for 3 hr. Water (100 mL) was added, and the mixture was extracted with ethyl acetate (150 mL). The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (100 mL), dried and concentrated to give the object compound (5.06 g) described in the above-mentioned scheme.

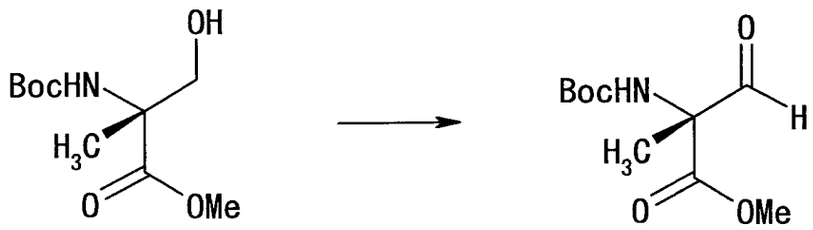
^{1}H-NMR ($CDCl_3$) δ: 5.29 (br s, 1H), 3.99 (dd, 1H, J = 11.6, 6.0

Hz), 3.83-3.73 (m, 1H), 3.78 (s, 3H), 3.23 (br s, 1H), 1.48 (s, 3H), 1.45 (s, 9H).

[0247]

step 2-7

[0248]



[0249]

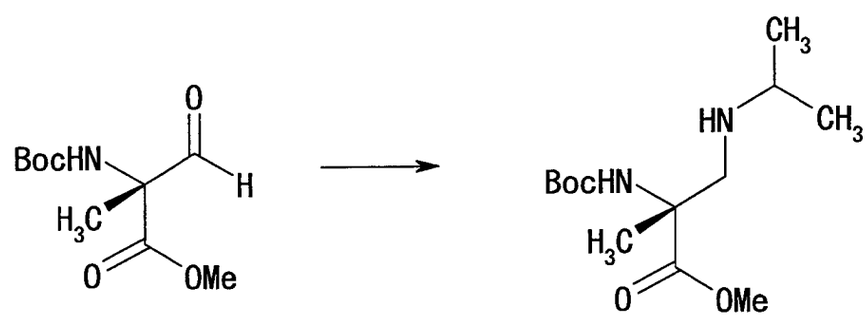
To a solution of the compound (2.50 g) obtained in step 2-6 in dimethyl sulfoxide (25 mL) were added triethylamine (2.25 mL) and a pyridine-sulfur trioxide complex (2.62 g), and the mixture was stirred at room temperature for 1 hr. 1N Aqueous hydrochloric acid solution (100 mL) was added, and the mixture was extracted with ethyl acetate (200 mL). The organic layer was washed successively with 1N aqueous hydrochloric acid solution (100 mL) and saturated aqueous sodium hydrogen carbonate solution (100 mL), dried and concentrated to give the object compound (1.22 g) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 9.57 (s, 1H), 5.63 (br s, 1H), 3.81 (s, 3H), 1.57 (s, 3H), 1.45 (s, 9H).

[0250]

step 2-8

[0251]



[0252]

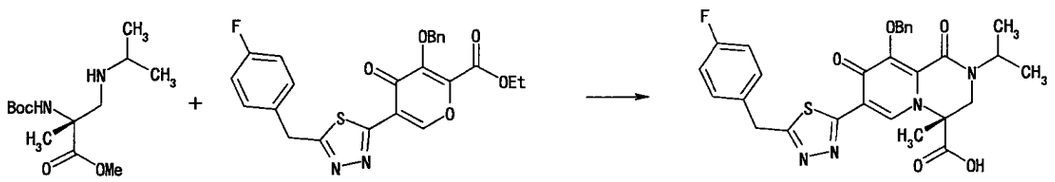
To a solution of the compound (660 mg) obtained in step 2-7 in chloroform (7.0 mL) were added isopropylamine (368 μL), acetic acid (245 μL) and sodium triacetoxyborohydride (955 mg), and the mixture was stirred at room temperature for 18 hr. Saturated aqueous sodium hydrogen carbonate solution (30 mL) and chloroform (50 mL) were added and the mixture was partitioned. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (30 mL), dried and concentrated. The concentrate was purified by silica gel column chromatography (chloroform:methanol=10:1) to give the object compound (764 mg) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 5.74 (br s, 1H), 3.74 (s, 3H), 2.89 (br s, 2H), 2.73 (sep, 1H, J = 6.2 Hz), 1.52 (s, 3H), 1.44 (s, 9H), 1.02 (d, 3H, J = 6.2 Hz), 1.02 (d, 3H, J = 6.2 Hz).

[0253]

step 2-9

[0254]



[0255]

The compound (155 mg) obtained in step 2-8 was dissolved in trifluoroacetic acid solution (1.0 mL), and the mixture was stirred at room temperature for 30 min. The mixture was concentrated, chloroform was added, and the mixture was concentrated. This operation was performed twice. Toluene (5 mL), diisopropylethylamine (395 μL) and the compound (200 mg) obtained in step 2-5 were added, and the mixture was stirred at room temperature for 30 min. Toluene (5 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (100 μL) were added, and the mixture was stirred at 120°C for 1 hr. The reaction mixture was allowed to cool to room temperature, acetic acid (1.0 mL) was added, and the mixture was further stirred at 110°C for 1

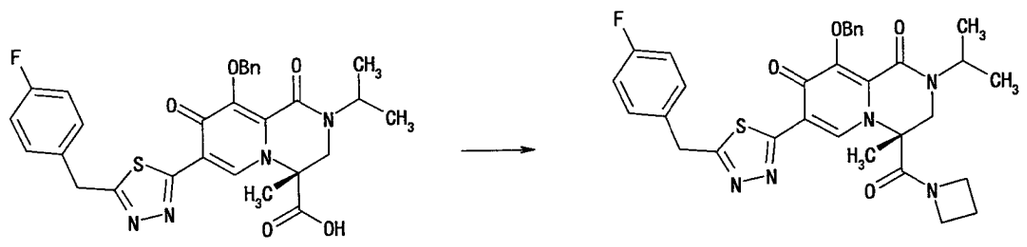
hr. 2N Aqueous hydrochloric acid solution (30 mL) was added, and the mixture was extracted with ethyl acetate (60 mL). The organic layer was dried and concentrated, toluene was added, and this operation was repeated twice to give the object compound (263 mg) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 8.87 (s, 1H), 7.59 (d, 2H, J = 7.0 Hz), 7.41-7.13 (m, 4H), 7.08-6.98 (m, 3H), 5.46 (d, 1H, J = 10.0 Hz), 5.23 (d, 1H, J = 10.0 Hz), 4.86 (sep, 1H, J = 6.3 Hz), 4.44 (s, 2H), 3.85 (d, 1H, J = 13.5 Hz), 3.44 (d, 1H, J = 13.5 Hz), 1.96 (s, 3H), 1.14 (d, 3H, J = 6.3 Hz), 1.12 (d, 3H, J = 6.3 Hz).

[0256]

step 2-10

[0257]



[0258]

To a solution of the compound (40.0 mg) obtained in step 2-9, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (28.0 mg) and 1-hydroxybenzotriazole hydrate (22.0 mg) in dimethylformamide (400 μL) was added azetidine (20 μL), and the mixture was stirred at room temperature for 18 hr. Saturated aqueous sodium hydrogen carbonate solution (10 mL) was added, and the mixture was extracted with ethyl acetate (25 mL). The organic layer was washed successively with 1N aqueous hydrochloric acid solution (10 mL) and saturated aqueous sodium hydrogen carbonate solution (10 mL), dried and concentrated. The concentrate was purified by silica gel thin layer chromatography (chloroform:methanol=15:1) to give the object compound (26.7 mg) described in the above-mentioned scheme.

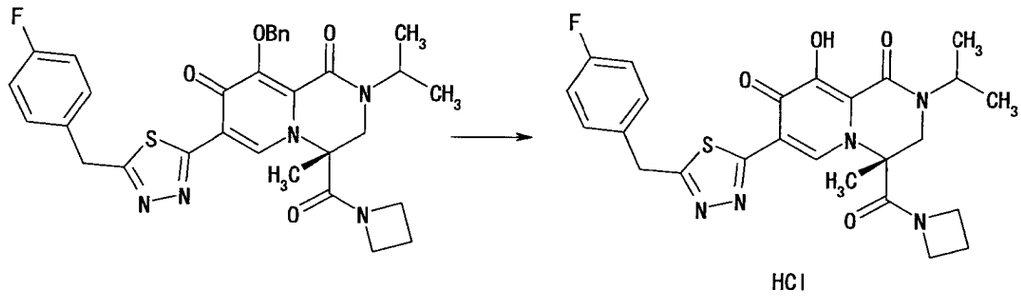
^{1}H-NMR ($CDCl_3$) δ: 8.99 (s, 1H), 7.64-7.58 (m, 2H), 7.36-7.27 (m,

5H), 7.07-6.99 (m, 2H), 5.53 (d, 1H, J = 10.0 Hz), 5.39 (d, 1H, J = 10.0 Hz), 4.82 (sep, 1H, J = 6.7 Hz), 4.46 (s, 2H), 4.10-3.92 (m, 2H), 3.97 (d, 1H, J = 13.4 Hz), 3.75-3.66 (m, 1H), 3.61-3.51 (m, 1H), 3.27 (d, 1H, J = 13.4 Hz), 2.19-2.05 (m, 2H), 1.97 (s, 3H), 1.15 (d, 6H, J = 6.7 Hz).

[0259]

step 2-11

[0260]



[0261]

The compound (25.0 mg) obtained in step 2-10 was dissolved in trifluoroacetic acid (1.0 mL), and the mixture was stirred at room temperature for 30 min. The reaction solution was concentrated, chloroform was added, and the mixture was concentrated. 4N Hydrochloric acid/ethyl acetate solution was added, and the mixture was concentrated. Crystallization from ethyl acetate-hexane gave the object compound (17.2 mg) described in the above-mentioned scheme. ^{1}H-NMR (DMSO-d_6) δ: 12.91 (br s, 1H), 8.71 (s, 1H), 7.46-7.38 (m, 2H), 7.23-7.15 (m, 2H), 4.70 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.29-4.18 (br m, 1H), 4.02 (d, 1H, J = 13.9 Hz), 3.90-3.81 (br m, 2H), 3.80-3.72 (br m, 1H), 3.71 (d, 1H, J = 13.9 Hz), 2.16-2.04 (br m, 2H), 1.99 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.14 (d, 3H, J = 6.7 Hz).

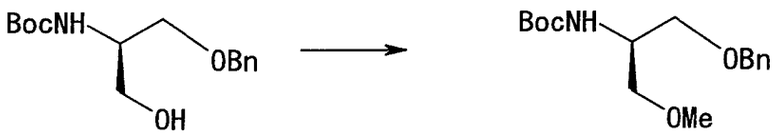
[0262]

Example 3

[0263]

step 3-1

[0264]



[0265]

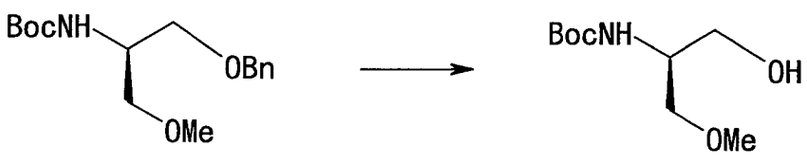
To a solution of (R)-1-benzyloxymethyl-2-hydroxyethylcarbamic acid tert-butyl ester (5.0 g) and 2,6-di-tert-butylpyridine (8.0 mL) in chloroform (50 mL) were added iodomethane (1.33 mL) and silver(I) trifluoromethanesulfonate (6.85 g) under ice-cooling, and the mixture was stirred for 30 min, and further stirred at room temperature for 1 hr. The reaction suspension was filtered through celite, and concentrated, and the concentrate was purified by silica gel column chromatography (ethyl acetate:hexane=1:20 - 1:4) to give the object compound (2.8 g) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 7.38-7.27 (m, 5H), 4.97-4.85 (m, 1H), 4.53 (s, 2H), 4.00-3.81 (m, 1H), 3.59 (dd, 1H, J = 9.4, 4.2 Hz), 3.51 (dd, 1H, J = 9.4, 5.8 Hz), 3.51 (dd, 1H, J = 9.4, 4.4 Hz), 3.44 (dd, 1H, J = 9.4, 6.0 Hz), 3.34 (s, 3H), 1.44 (s, 9H).

[0266]

step 3-2

[0267]



[0268]

To a solution of the compound (2.8 g) obtained in step 3-1 in methanol (100 mL) was added a 7.5% palladium-carbon catalyst (1.4 g), and the mixture was stirred at room temperature for 17 hr under a hydrogen atmosphere and moderate pressure (0.4 MPa). The reaction mixture was filtered through celite and concentrated to give the object compound (2.05 g) described in the above-mentioned scheme.

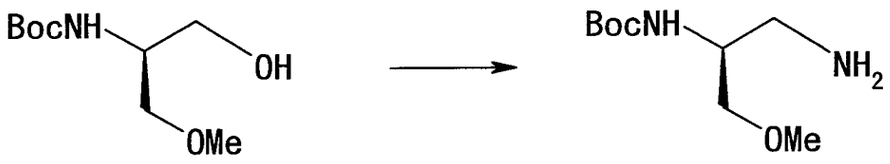
^{1}H-NMR ($CDCl_3$) δ: 5.22-5.10 (m, 1H), 3.84-3.64 (m, 3H), 3.60-

3.49 (m, 2H), 3.37 (s, 3H), 2.73-2.55 (m, 1H), 1.45 (s, 9H).

[0269]

step 3-3

[0270]



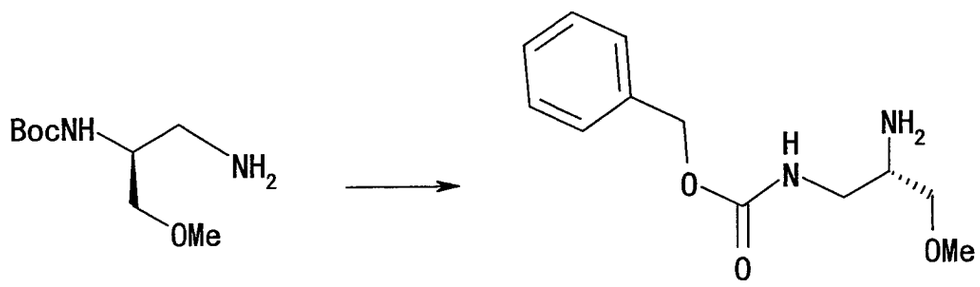
[0271]

To a solution of the compound (1.6 g) obtained in step 3-2, phthalimide (1.38 g) and triphenylphosphine (2.47 g) in tetrahydrofuran (20 mL) was added dropwise 2.2M diethyl azodicarboxylate/toluene solution (4.3 mL) under ice-cooling, and the mixture was stirred at room temperature for 20 min. The reaction mixture was concentrated, and the concentrate was purified by silica gel column chromatography (ethyl acetate:hexane=1:10 - 1:2). The obtained solid was dissolved in ethanol (30 mL)-toluene (30 mL), hydrazine monohydrate (1.6 mL) was added, and the mixture was stirred at 80°C for 40 min. The mixture was allowed to cool to room temperature, the solid was filtered off, and the filtrate was concentrated. Toluene was added to the residue, and the precipitated solid was filtered off. The filtrate was concentrated to give the object compound (1.3 g) described in the above-mentioned scheme. ^{1}H-NMR ($CDCl_3$) δ: 5.08-4.89 (m, 1H), 3.71-3.63 (m, 1H), 3.50 (dd, 1H, J = 9.5, 3.7 Hz), 3.40 (dd, 1H, J = 9.5, 5.1 Hz), 3.35 (s, 3H), 2.84 (dd, 1H, J = 13.0, 6.0 Hz), 2.80 (dd, 1H, J= 13.0, 6.0 Hz), 1.45 (s, 9H).

[0272]

step 3-4

[0273]



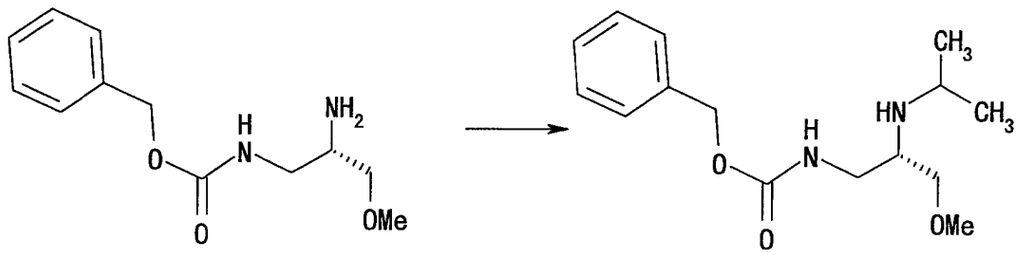
[0274]

To a solution of the compound (0.8 g) obtained in step 3-3 in dioxane (8 mL) was added saturated aqueous sodium hydrogen carbonate solution (2 mL), benzyl chloroformate (0.84 mL) was added dropwise under ice-cooling, and the mixture was stirred for 40 min, and at room temperature for 10 min. Water (15 mL) was added, and the mixture was extracted with ethyl acetate. The extract was dried, and concentrated, and the concentrate was purified by silica gel column chromatography (ethyl acetate:hexane=1:10 - 1:2). To the obtained solid was added 4N hydrochloric acid/dioxane solution (5 mL), and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated, and the residue was dissolved in chloroform. Saturated aqueous sodium hydrogen carbonate solution (2 mL) was added, and the mixture was stirred. The mixture was extracted with chloroform, and the organic layer was dried and concentrated to give the object compound (639 mg) described in the above-mentioned scheme.
^{1}H-NMR ($CDCl_3$) δ: 7.39-7.28 (m, 5H), 5.27-5.20 (m, 1H), 5.10 (s, 2H), 3.41-3.24 (m, 3H), 3.35 (s, 3H), 3.18-3.01 (m, 2H), 1.39 (br s, 2H).

[0275]

step 3-5

[0276]



[0277]

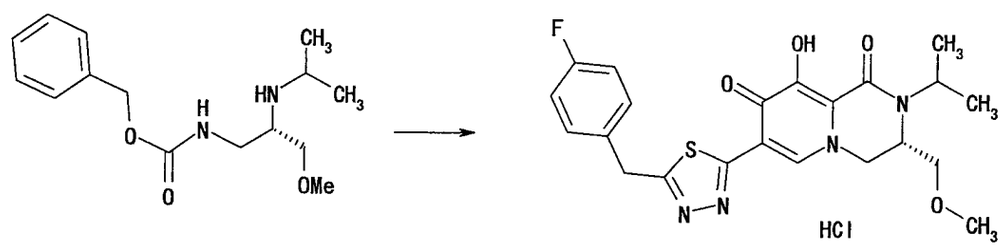
To a solution of the compound (150 mg) obtained in step 3-4 in chloroform (4 mL) were added acetone (70 μL), acetic acid (54 μL) and sodium triacetoxyborohydride (200 mg) under ice-cooling, and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with chloroform, saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was stirred. The chloroform layer was washed with saturated brine, dried, and concentrated to give the object compound (156 mg) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 7.39-7.28 (m, 5H), 5.39-5.29 (m, 1H), 5.10 (s, 2H), 3.42-3.28 (m, 3H), 3.33 (s, 3H), 3.22-3.14 (m, 1H), 2.96-2.82 (m, 2H), 1.04 (d, 3H, J = 6.8 Hz), 1.02 (d, 3H, J = 6.8 Hz).

[0278]

step 3-6

[0279]



[0280]

In the same manner as in step 2-9 and step 2-11, the object compound (17.0 mg) described in the above-mentioned scheme was obtained from the compound (156 mg) obtained in step 3-5. For removal of the amino-protecting group (benzyloxycarbonyl group) of the compound obtained in step 3-5,

a known method was used according to the protecting group. ^{1}H-NMR (DMSO-d_6) δ: 8.84 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.14 (m, 2H), 4.66 (d, 1H, J = 13.2 Hz), 4.47 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 4.34 (dd, 1H, J = 13.5, 3.7 Hz), 4.22-4.17 (m, 1H), 3.49 (dd, 1H, J = 10.6, 4.3 Hz), 3.39 (dd, 1H, J = 10.6, 7.5 Hz), 3.21 (s, 3H), 1.30 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).

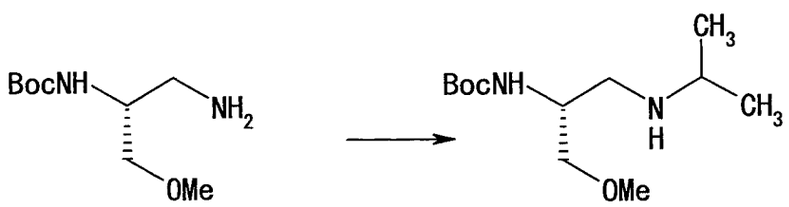
[0281]

Example 4

[0282]

step 4-1

[0283]



[0284]

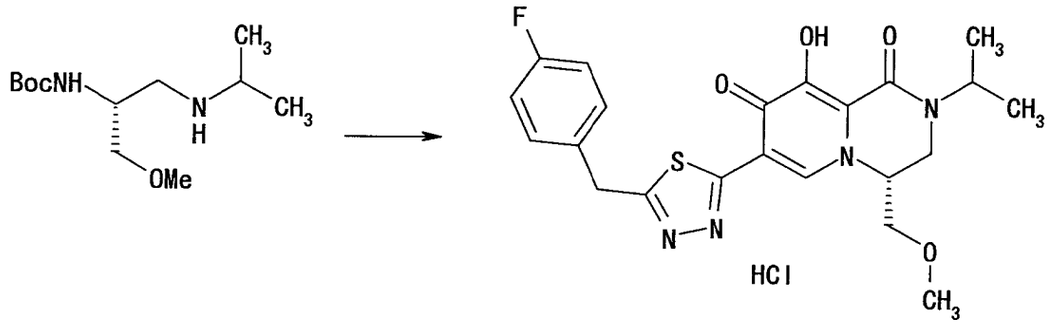
To a solution of (R)-1-aminomethyl-2-methoxyethylcarbamic acid tert-butyl ester (1.0 g) produced from (S)-1-benzyloxymethyl-2-hydroxyethylcarbamic acid tert-butyl ester in the same manner as in Example 3, step 3-1 to step 3-3 in chloroform (15 mL) were added acetone (432 μL) and acetic acid (337 μL) under ice-cooling, sodium triacetoxyborohydride (1.25 g) was added at room temperature, and the mixture was stirred at room temperature for 14 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted 3 times with chloroform. The combined chloroform layer was dried, and concentrated, and the concentrate was purified by silica gel column chromatography (chloroform:methanol=50:1 - 7:1) to give the object compound (1.12 g) described in the above-mentioned scheme. ^{1}H-NMR ($CDCl_3$) δ: 5.09-4.90 (m, 1H), 3.81-3.69 (m, 1H), 3.49 (dd, 1H, J = 9.5, 4.0 Hz), 3.43-3.37 (m, 1H), 3.34 (s, 3H), 2.82-2.68 (m, 3H), 1.45 (s, 9H), 1.04 (d, 3H, J = 6.4 Hz),

1.03 (d, 3H, J = 6.4 Hz).

[0285]

step 4-2

[0286]



[0287]

In the same manner as in step 2-9 and step 2-11 (known deprotection and condensation reactions may be omitted as necessary), the object compound (10.8 mg) described in the above-mentioned scheme was obtained from the compound (19.0 mg) obtained in step 4-1.

^{1}H-NMR (DMSO-d_6) δ: 12.82 (br s, 1H), 8.80 (s, 1H), 7.45-7.38 (m, 2H), 7.23-7.15 (m, 2H), 5.01-4.93 (m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 3.84 (dd, 1H, J = 13.8, 4.1 Hz), 3.75 (dd, 1H, J = 13.8, 1.3 Hz), 3.65-3.54 (m, 2H), 3.25 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).

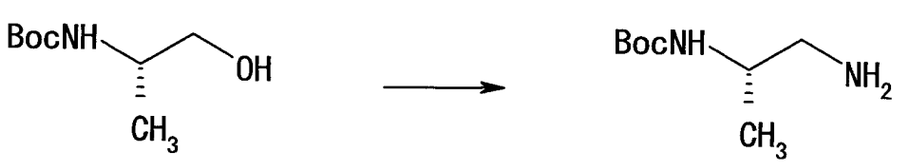
[0288]

Example 5

[0289]

step 5-1

[0290]



[0291]

In the same manner as in step 3-3, the object compound (1.0 g) described in the above-mentioned scheme was obtained from (S)-2-hydroxy-1-methylethylcarbamic acid tert-butyl ester

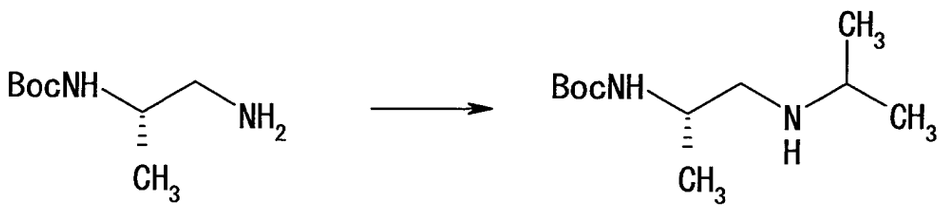
(1.4 g).

^{1}H-NMR ($CDCl_3$) δ: 4.68-4.49 (m, 1H), 3.71-3.58 (m, 1H), 2.74 (dd, 1H, J = 13.0, 4.9 Hz), 2.62 (dd, 1H, J = 13.0, 6.5 Hz), 1.45 (s, 9H), 1.12 (d, 3H, J= 6.7 Hz).

[0292]

step 5-2

[0293]



[0294]

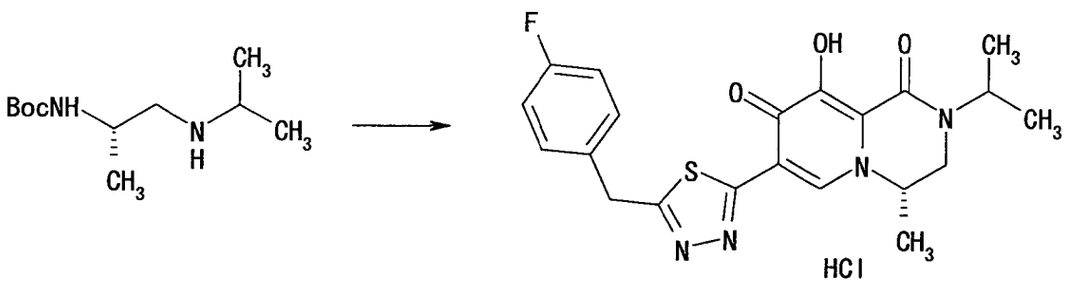
In the same manner as in step 4-1, the object compound (180 mg) described in the above-mentioned scheme was obtained from the compound (190 mg) obtained in step 5-1.

^{1}H-NMR ($CDCl_3$) δ: 4.91-4.66 (m, 1H), 3.81-3.66 (m, 1H), 2.81 (sep, 1H, J = 6.4 Hz), 2.66 (dd, 1H, J = 12.0, 4.9 Hz), 2.60 (dd, 1H, J = 12.0, 6.7 Hz), 1.45 (s, 9H), 1.14 (d, 3H, J = 6.6 Hz), 1.06 (d, 6H, J = 6.4 Hz).

[0295]

step 5-3

[0296]



[0297]

In the same manner as in step 2-9 and step 2-11, the object compound (27.5 mg) described in the above-mentioned scheme was obtained from the compound (30.0 mg) obtained in step 5-2.

^{1}H-NMR (DMSO-d_6) δ: 12.81 (br s, 1H), 8.91 (s, 1H), 7.45-7.38

(m, 2H), 7.22-7.15 (m, 2H), 4.92 (ddd, 1H, J = 6.8, 3.5, 2.2 Hz), 4.80 (t, 1H, J = 6.8 Hz), 4.47 (s, 2H), 3.81 (dd, 1H, J = 13.5, 3.5 Hz), 3.63 (dd, 1H, J = 13.5, 2.2 Hz), 1.39 (d, 3H, J = 6.8 Hz), 1.19 (d, 3H, J = 6.8 Hz), 1.16 (d, 3H, J = 6.8 Hz).

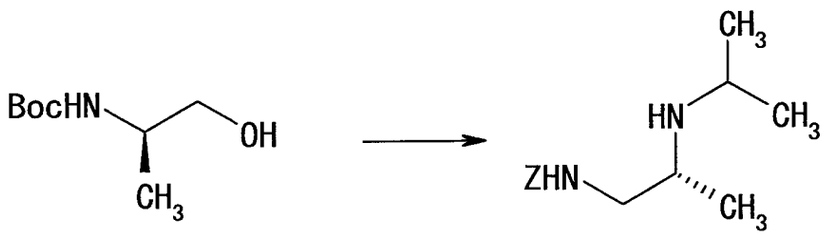
[0298]

Example 6

[0299]

step 6-1

[0300]



[0301]

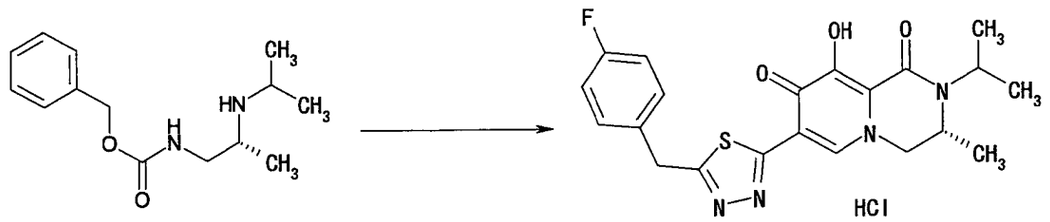
In the same manner as in step 3-3 to step 3-5, the object compound (105 mg) described in the above-mentioned scheme was obtained from (R)-2-hydroxy-1-methylethylcarbamic acid tert-butyl ester (2.0 g).

^{1}H-NMR ($CDCl_3$) δ: 7.40-7.28 (m, 5H), 5.28 (br s, 1H), 5.10 (s, 2H), 3.29-3.17 (m, 1H), 3.02-2.92 (m, 1H), 2.92-2.80 (m, 2H), 1.04 (d, 6H, J = 6.3 Hz), 0.99 (d, 3H, J = 6.0 Hz).

[0302]

step 6-2

[0303]



[0304]

In the same manner as in step 2-9 and step 2-11 (known deprotection and condensation reactions may be omitted as necessary), the object compound (16.6 mg) described in the above-mentioned scheme was obtained from the compound (105 mg)

obtained in step 6-1. For removal of the amino-protecting group (benzyloxycarbonyl group) of the compound obtained in step 6-1, a known method was used according to the protecting group.

^{1}H-NMR (DMSO-d_6) δ: 12.54 (br s, 1H), 8.85 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.62-4.53 (m, 1H), 4.51-4.44 (m, 3H), 4.32 (dd, 1H, J = 13.1, 3.4 Hz), 4.26-4.18 (m, 1H), 1.27 (d, 3H, J = 6.7 Hz), 1.26 (d, 3H, J = 6.7 Hz), 1.21 (d, 3H, J = 6.5 Hz).

[0305]

Example 7

[0306]

step 7-1

[0307]



[0308]

2-Amino-2-methyl-1,3-propanediol (20.0 g) was suspended in tetrahydrofuran (400 mL), and di-tert-butyl dicarbonate (41.6 g) was added. The mixture was stirred at room temperature for 3 hr and concentrated. Dimethylformamide (200 mL) was added to dissolve the concentrate again, imidazole (13.0 g) and tert-butylchlorodimethylsilane (29.3 g) were added, and the mixture was stirred at room temperature for 15 hr. Water (500 mL) was added, and the mixture was extracted with ethyl acetate (800 mL). The organic layer was washed with water (400 mL), dried, and concentrated. The concentrate was purified by silica gel column chromatography (ethyl acetate:hexane=1:10) to give the object compound (35.9 g) described in the above-mentioned scheme.

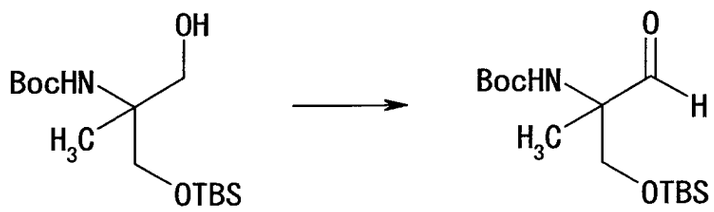
^{1}H-NMR ($CDCl_3$) δ: 5.13 (br s, 1H), 4.00 (br s, 1H), 3.77 (d, 1H, J = 9.7 Hz), 3.70 (dd, 1H, J = 11.4, 4.2 Hz), 3.61 (d, 1H, J =

9.7 Hz), 3.55 (dd, 1H, J = 11.4, 8.4 Hz), 1.44 (s, 9H), 1.19 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

[0309]

step 7-2

[0310]



[0311]

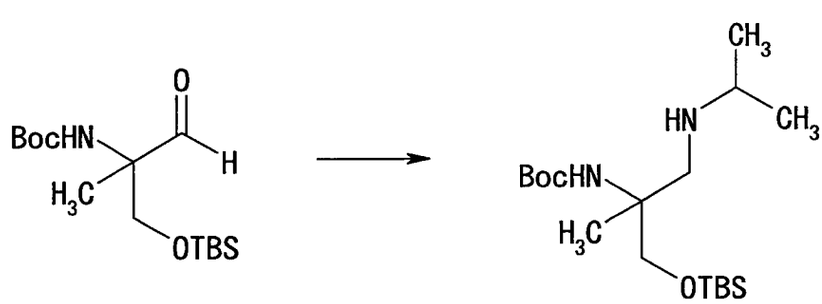
To a solution of the compound (15.5 g) obtained in step 7-1 in dimethyl sulfoxide (120 mL) were added triethylamine (8.12 mL) and a sulfur trioxide-pyridine complex (11.9 g), and the mixture was stirred at room temperature for 3 hr. 1N Aqueous hydrochloric acid solution (300 mL) was added, and the mixture was extracted with ethyl acetate (700 mL). The organic layer was washed successively with 1N aqueous hydrochloric acid solution (150 mL) and saturated aqueous sodium hydrogen carbonate solution (200 mL), dried, and concentrated. The concentrate was purified by silica gel column chromatography (ethyl acetate:hexane=1:20) to give the object compound (11.0 g) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 9.49 (s, 1H), 5.29 (br s, 1H), 3.86-3.71 (br m, 2H), 1.45 (s, 9H), 1.34 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H).

[0312]

step 7-3

[0313]



[0314]

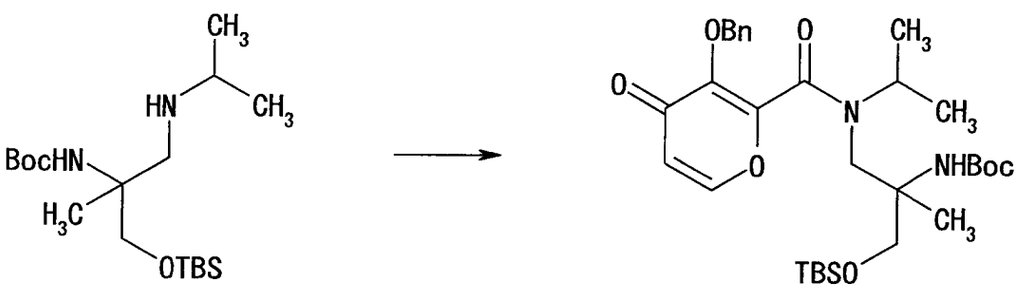
To a solution of the compound (11.0 g) obtained in step 7-2 in chloroform (110 mL) were added isopropylamine (4.46 mL), acetic acid (2.97 mL) and sodium triacetoxyborohydride (11.6 g), and the mixture was stirred at room temperature for 15 hr. The mixture was partitioned between saturated aqueous sodium hydrogen carbonate solution (150 mL) and chloroform (200 mL). The organic layer was washed twice with saturated aqueous sodium hydrogen carbonate solution (100 mL), dried, and concentrated. The concentrate was purified by silica gel column chromatography (chloroform:methanol=10:1) to give the object compound (14.1 g) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 5.43 (br s, 1H), 3.73 (d, 1H, J = 9.6 Hz), 3.58 (d, 1H, J = 9.6 Hz), 2.80-2.66 (m, 2H), 2.55 (d, 1H, J = 11.6 Hz), 1.43 (s, 9H), 1.24 (s, 3H), 1.05 (br s, 6H), 0.89 (s, 9H), 0.05 (s, 6H).

[0315]

step 7-4

[0316]



[0317]

To a solution of 3-benzyloxy-4-oxo-4H-pyran-2-carboxylic acid (5.00 g) in toluene (100 mL) were added triethylamine (3.40 mL) and thionyl chloride (1.78 mL) at 0°C, and the mixture was stirred at 0°C for 30 min. The precipitated salt was filtered off, the filtrate was concentrated, and the concentrate was dissolved in tetrahydrofuran (40 mL). This tetrahydrofuran solution was added dropwise to a solution of the compound (10.3 g) obtained in step 7-3 and pyridine (30 mL) in tetrahydrofuran (60 mL) at 0°C, and the mixture was

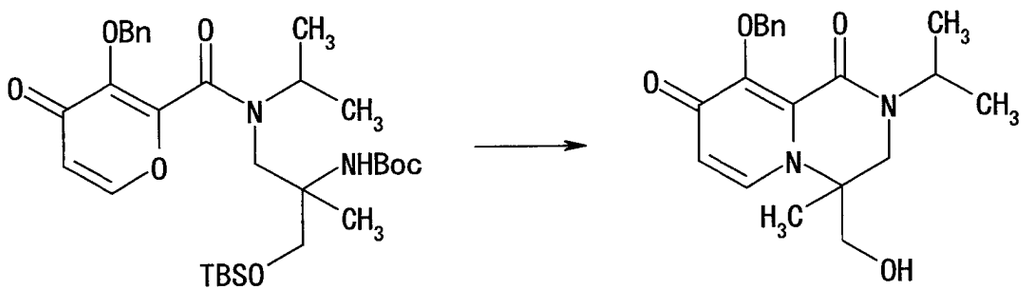
stirred at room temperature for 30 min. The reaction mixture was concentrated, toluene was added and the mixture was concentrated. This operation was performed twice. 1N Aqueous hydrochloric acid solution (150 mL) was added, and the mixture was extracted with ethyl acetate (250 mL). The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (100 mL), dried, and concentrated. The concentrate was purified by silica gel column chromatography (chloroform:methanol=50:1) to give the object compound (9.65 g) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 7.74-7.66 (m, 1H), 7.46-7.28 (m, 5H), 6.50-6.42 (m, 1H), 5.96 (br s, 1H), 5.28-5.14 (m, 2H), 4.02-3.33 (m, 5H), 1.47-1.37 (m, 9H), 1.29-1.00 (m, 9H), 0.95-0.83 (m, 9H), 0.13-0.03 (m, 6H).

[0318]

step 7-5

[0319]



[0320]

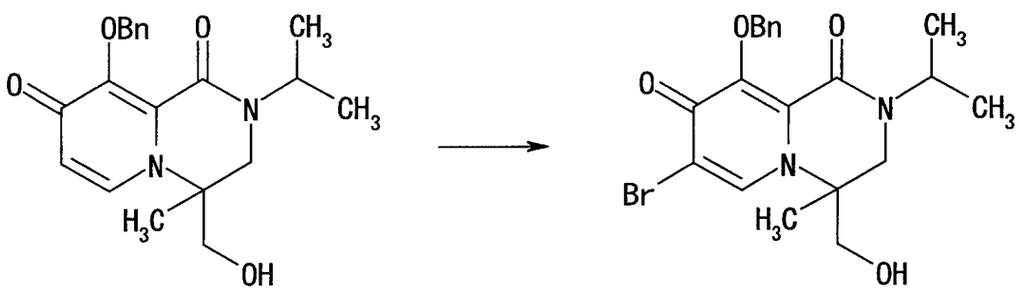
To the compound (9.65 g) obtained in step 7-4 was added 4N hydrochloric acid/ethyl acetate solution (100 mL), and the mixture was stirred at room temperature for 30 min. This was concentrated, ethanol (400 mL) and saturated aqueous sodium hydrogen carbonate solution (100 mL) were added, and the mixture was stirred at room temperature for 18 hr. The insoluble material was filtered off, and the filtrate was concentrated. Water (100 mL) was added, and the mixture was extracted twice with chloroform (200 mL, 100 mL). The organic layer was dried, and concentrated, and the concentrate was purified by silica gel column chromatography

(chloroform:methanol=30:1 - 20:1 - 10:1) to give the object compound (2.20 g) described in the above-mentioned scheme. ^{1}H-NMR ($CDCl_3$) δ: 7.52 (d, 2H, J = 7.9 Hz), 7.48 (d, 1H, J = 7.9 Hz), 7.37-7.22 (m, 3H), 6.25 (d, 1H, J = 7.9 Hz), 5.79 (br s, 1H), 5.20 (d, 1H, J = 10.0 Hz), 5.17 (d, 1H, J = 10.0 Hz), 4.85 (sep, 1H, J = 6.5 Hz), 3.80 (d, 1H, J = 12.1 Hz), 3.61 (d, 1H, J = 12.1 Hz), 3.35 (d, 1H, J = 14.2 Hz), 3.14 (d, 1H, J = 14.2 Hz), 1.47 (s, 3H), 1.12 (d, 3H, J = 6.5 Hz), 1.11 (d, 3H, J = 6.5 Hz).

[0321]

step 7-6

[0322]



[0323]

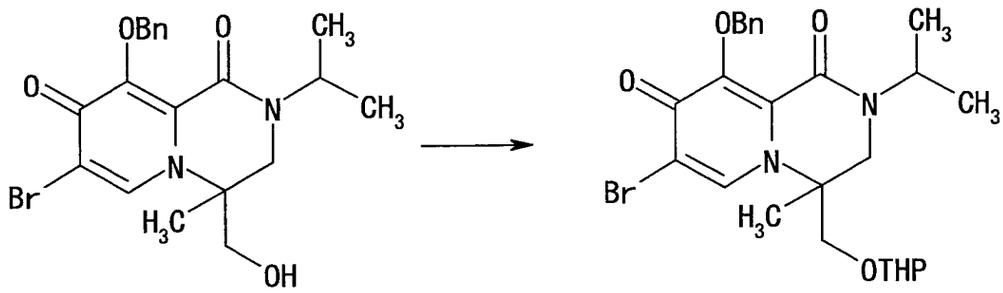
The compound (2.20 g) obtained in step 7-5, trimethylphenylammonium tribromide (3.48 g) and sodium hydrogen carbonate (1.04 g) were dissolved in 2:1 chloroform-methanol (60 mL), and the mixture was stirred at room temperature for 30 min. Saturated aqueous sodium hydrogen carbonate solution (100 mL) was added, and the mixture was extracted with chloroform (200 mL). The organic layer was washed successively with 1N aqueous hydrochloric acid solution (100 mL) and saturated aqueous sodium hydrogen carbonate solution (100 mL), dried, and concentrated to give the object compound (2.23 g) described in the above-mentioned scheme. ^{1}H-NMR (DMSO-d_6) δ: 8.22 (s, 1H), 7.53 (d, 2H, J = 7.0 Hz), 7.41-7.27 (m, 3H), 5.48 (br s, 1H), 5.10 (d, 1H, J = 10.2 Hz), 5.03 (d, 1H, J = 10.2 Hz), 4.67 (sep, 1H, J = 6.7 Hz), 3.66 (d, 1H, J = 11.6 Hz), 3.59 (d, 1H, J = 11.6 Hz), 3.56 (d, 1H, J = 14.2 Hz), 3.45 (d, 1H, J = 14.2 Hz), 1.48 (s, 3H), 1.11 (d, 6H,

J = 6.7 Hz).

[0324]

step 7-7

[0325]



[0326]

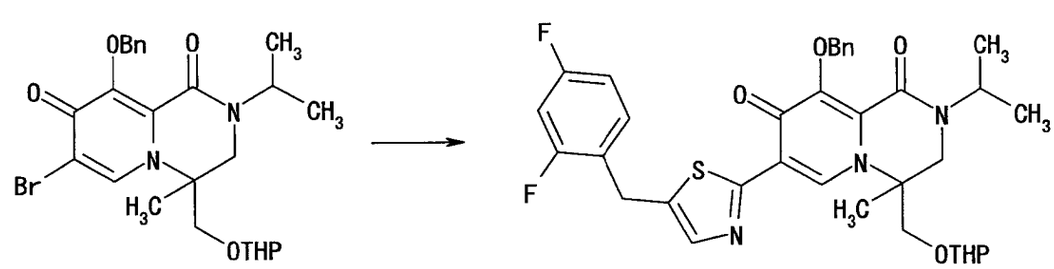
To a solution of the compound (2.12 g) obtained in step 7-6 in chloroform (45 mL) were added 3,4-dihydro-2H-pyran (882 μL) and camphorsulfonic acid (56 mg), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated, and the concentrate was purified by silica gel column chromatography (chloroform:methanol=30:1) to give the object compound (2.23 g) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 7.91-7.89 (m, 1H), 7.72-7.66 (m, 2H), 7.37-7.27 (m, 3H), 5.41-5.36 (m, 1H), 5.27-5.17 (m, 1H), 5.02-4.92 (m, 1H), 4.61-4.48 (m, 1H), 3.92-3.81 (m, 1H), 3.79-3.27 (m, 5H), 1.78-1.48 (m, 9H), 1.20-1.14 (m, 6H).

[0327]

step 7-8

[0328]



[0329]

The compound (250 mg) obtained in step 7-7, tris(dibenzylideneacetone)dipalladium (44 mg), tri(2-

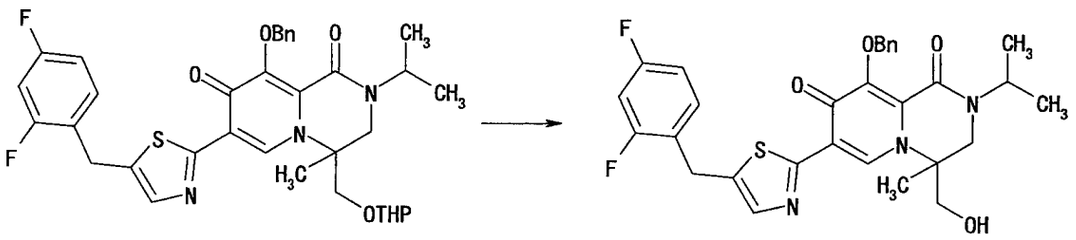
furyl)phosphine (45 mg) and 5-(2,4-difluorobenzyl)-2-tributylstanylthiazole (835 mg) were dissolved in dioxane (5.0 mL), and the mixture was heated in a microwave apparatus at 110°C for 40 min. This operation was performed twice using the same amounts, and the reaction mixtures were combined and concentrated. The concentrate was purified by silica gel column chromatography (chloroform:methanol=30:1) to give the object compound (682 mg) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 8.78-8.74 (m, 1H), 7.72-7.67 (m, 2H), 7.60-7.56 (m, 1H), 7.37-7.17 (m, 4H), 6.86-6.71 (m, 2H), 5.52-5.46 (m, 1H), 5.34-5.25 (m, 1H), 5.03-4.93 (m, 1H), 4.62-4.53 (m, 1H), 4.20-4.14 (m, 2H), 4.02-3.87 (m, 1H), 3.77-3.43 (m, 5H), 3.36-3.26 (m, 1H), 1.78-1.42 (m, 8H), 1.21-1.13 (m, 6H).

[0330]

step 7-9

[0331]



[0332]

The compound (682 mg) obtained in step 7-8 was dissolved in tetrahydrofuran-methanol-water (4:1:1, 6.0 mL). Acetic acid (2.0 mL) was added, and the mixture was stirred at 80°C for 30 hr. The reaction mixture was concentrated, toluene was added, and the mixture was concentrated. This operation was performed twice, and the concentrate was purified by silica gel column chromatography (chloroform:methanol=40:1) to give the object compound (390 mg) described in the above-mentioned scheme.

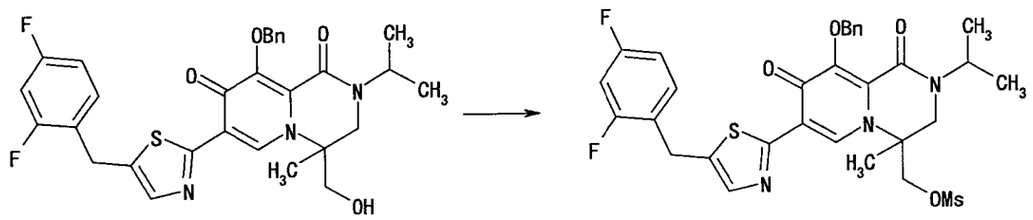
^{1}H-NMR ($CDCl_3$) δ: 8.66 (s, 1H), 7.67-7.62 (m, 2H), 7.51 (s, 1H), 7.36-7.25 (m, 3H), 7.24-7.15 (m, 1H), 6.84-6.75 (m, 2H), 5.40 (d, 1H, J = 9.7 Hz), 5.29 (d, 1H, J = 9.7 Hz), 4.93 (sep, 1H, J = 6.7 Hz), 4.14 (s, 2H), 3.86 (s, 2H), 3.51 (d, 1H, J = 13.9

Hz), 3.25 (d, 1H, J = 13.9 Hz), 1.65 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.15 (d, 3H, J = 6.7 Hz).

[0333]

step 7-10

[0334]



[0335]

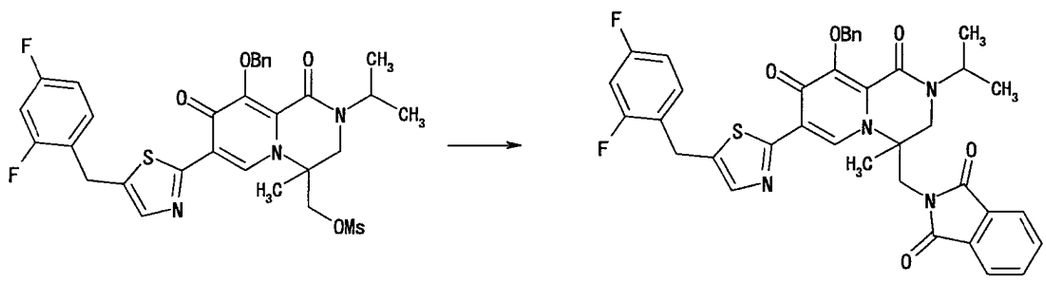
To a solution of the compound (250 mg) obtained in step 7-9 in chloroform (5.0 mL) were added triethylamine (93 μL) and methanesulfonyl chloride (41 μL) at 0°C, and the mixture was stirred at 0°C for 1 hr. Triethylamine (93 μL) and methanesulfonyl chloride (41 μL) were added, and the mixture was further stirred at 0°C for 1 hr. Saturated aqueous sodium hydrogen carbonate solution (20 mL) was added, and the mixture was extracted with chloroform (40 mL). The organic layer was washed with 1N aqueous hydrochloric acid solution (20 mL), dried, and concentrated to give the object compound (295 mg) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 7.68-7.61 (m, 4H), 7.40-7.20 (m, 4H), 6.92-6.82 (m, 2H), 5.45 (d, 1H, J = 9.8 Hz), 5.32 (d, 1H, J = 9.8 Hz), 4.98 (sep, 1H, J = 6.8 Hz), 4.80 (br s, 1H), 4.50 (d, 1H, J = 10.1 Hz), 4.19 (s, 2H), 3.58 (d, 1H, J = 14.1 Hz), 3.37 (d, 1H, J = 14.1 Hz), 3.20 (br s, 3H), 1.85 (s, 3H), 1.22 (d, 3H, J = 6.8 Hz), 1.19 (d, 3H, J = 6.8 Hz).

[0336]

step 7-11

[0337]



[0338]

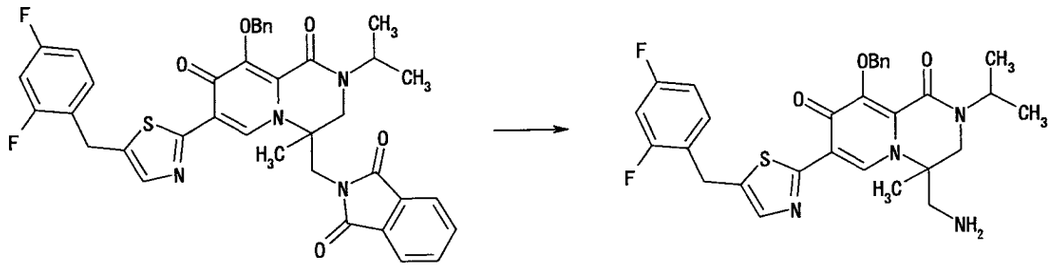
The compound (30 mg) obtained in step 7-10 and potassium phthalimide (26 mg) were dissolved in dimethylformamide (1.0 mL), and the mixture was heated in a microwave apparatus at 150°C for 2 hr. This operation was performed two more times using the compound (115 mg) obtained in step 7-10, potassium phthalimide (100 mg) and dimethylformamide (4.0 mL), and all the reaction mixtures were combined. Water (30 mL) was added, and the mixture was extracted with ethyl acetate (60 mL). The organic layer was washed successively with 1N aqueous hydrochloric acid solution (30 mL) and saturated aqueous sodium hydrogen carbonate solution (30 mL), dried and concentrated. The concentrate was purified by silica gel column chromatography (chloroform:methanol=30:1) to give the object compound (277 mg) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 8.45 (s, 1H), 7.91-7.58 (m, 7H), 7.40-7.14 (m, 4H), 6.85-6.76 (m, 2H), 5.60 (d, 1H, J = 9.7 Hz), 5.31 (d, 1H, J = 9.7 Hz), 5.07 (sep, 1H, J = 6.7 Hz), 4.21 (d, 1H, J = 14.4 Hz), 4.12 (s, 2H), 3.88 (d, 1H, J = 14.4 Hz), 3.58 (d, 1H, J = 13.9 Hz), 3.47 (d, 1H, J = 13.9 Hz), 1.78 (s, 3H), 1.29 (d, 3H, J = 6.7 Hz), 1.21 (d, 3H, J = 6.7 Hz).

[0339]

step 7-12

[0340]



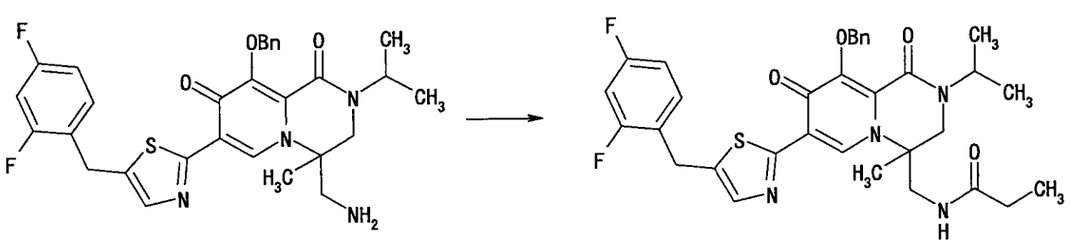
[0341]

To a solution of the compound (277 mg) obtained in step 7-11 in 1:1 ethanol-toluene (6.0 mL) was added hydrazine monohydrate (60 μL), and the mixture was stirred at 80°C for 3 hr. Furthermore, hydrazine monohydrate (60 μL) was added, and the mixture was stirred at 80°C for 2 hr. The precipitate was filtered off, and the filtrate was concentrated, and the concentrate was purified by silica gel column chromatography (chloroform:methanol=30:1 - 20:1) to give the object compound (104 mg) described in the above-mentioned scheme.
^{1}H-NMR ($CDCl_3$) δ: 8.71 (s, 1H), 7.71-7.63 (m, 2H), 7.59 (s, 1H), 7.38-7.27 (m, 3H), 7.25-7.16 (m, 1H), 6.85-6.76 (m, 2H), 5.53 (d, 1H, J = 9.7 Hz), 5.26 (d, 1H, J = 9.7 Hz), 4.97 (sep, 1H, J = 6.7 Hz), 4.18 (s, 2H), 3.51 (d, 1H, J = 13.9 Hz), 3.32 (d, 1H, J = 13.9 Hz), 3.05 (d, 1H, J = 13.7 Hz), 2.98 (d, 1H, J = 13.7 Hz), 1.67 (s, 3H), 1.20 (d, 3H, J = 6.7 Hz), 1.18 (d, 3H, J = 6.7 Hz).

[0342]

step 7-13

[0343]



[0344]

To a solution of the compound (20.0 mg) obtained in step 7-12 in chloroform (400 μL) were added triethylamine (9.9 μL) and propionyl chloride (4.8 μL), and the mixture was stirred at

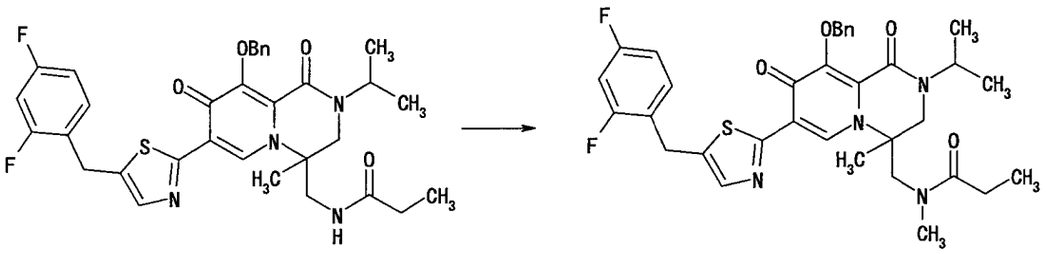
room temperature for 1 hr. The obtained reaction mixture was directly purified by silica gel thin layer chromatography (chloroform:methanol=10:1) to give the object compound (14.2 mg) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 8.58 (s, 1H), 7.64-7.59 (m, 2H), 7.52 (s, 1H), 7.36-7.27 (m, 3H), 7.25-7.17 (m, 1H), 6.86-6.78 (m, 2H), 6.21 (br s, 1H), 5.40 (d, 1H, J = 9.7 Hz), 5.28 (d, 1H, J = 9.7 Hz), 4.96 (sep, 1H, J = 6.7 Hz), 4.15 (s, 2H), 3.76 (dd, 1H, J = 14.7, 7.1 Hz), 3.55 (dd, 1H, J = 14.7, 6.4 Hz), 3.39 (d, 1H, J = 13.7 Hz), 3.35 (d, 1H, J = 13.7 Hz), 2.28 (dt, 2H, J = 14.5, 6.6 Hz), 1.61 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz), 1.14 (t, 3H, J = 7.7 Hz).

[0345]

step 7-14

[0346]



[0347]

To a solution of the compound (14.0 mg) obtained in step 7-13 in tetrahydrofuran (1.0 mL) were added excess amounts of iodomethane and potassium tert-butoxide at 0°C (until disappearance of starting materials). The obtained reaction mixture was directly purified by silica gel thin layer chromatography (chloroform:methanol=15:1) to give the object compound (5.6 mg) described in the above-mentioned scheme.

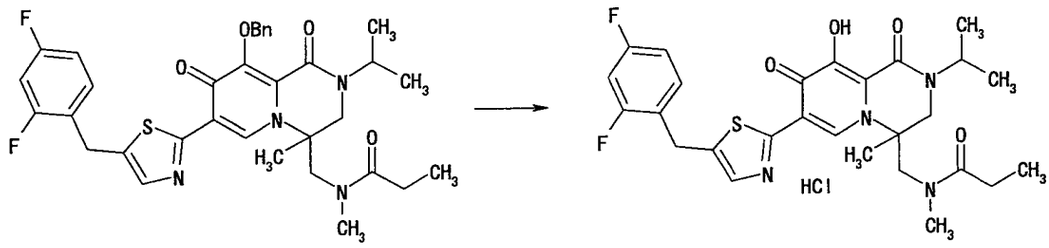
^{1}H-NMR ($CDCl_3$) δ: 8.60 (s, 1H), 7.68-7.63 (m, 2H), 7.58 (s, 1H), 7.36-7.27 (m, 3H), 7.25-7.19 (m, 1H), 6.86-6.77 (m, 2H), 5.58 (d, 1H, J = 10.0 Hz), 5.32 (d, 1H, J = 10.0 Hz), 4.98 (sep, 1H, J = 6.7 Hz), 4.28 (d, 1H, J = 14.4 Hz), 4.19 (s, 2H), 3.47 (d, 1H, J = 14.2 Hz), 3.32 (d, 1H, J = 14.2 Hz), 3.12 (d, 1H, J = 14.4 Hz), 2.54 (s, 3H), 2.37 (dq, 1H, J = 15.5, 7.0 Hz), 2.30

(dq, 1H, J = 15.5, 7.0 Hz), 1.69 (s, 3H), 1.21 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz), 1.15 (t, 3H, J = 7.0 Hz).

[0348]

step 7-15

[0349]



[0350]

The compound (5.6 mg) obtained in step 7-14 was dissolved in trifluoroacetic acid (1.0 mL), and the mixture was stirred at room temperature for 1 hr. The reaction solution was concentrated, chloroform was added, and the mixture was concentrated. 4N Hydrochloric acid/ethyl acetate solution was added, and the mixture was concentrated. Crystallization from ethyl acetate-hexane gave the object compound (3.2 mg) described in the above-mentioned scheme.

^{1}H-NMR (DMSO-d_6) δ: 13.18 (br s, 1H), 8.41 (s, 1H), 7.65 (s, 1H), 7.44 (td, 1H, J = 8.8, 6.7 Hz), 7.25 (ddd, 1H, J = 10.2, 9.3, 2.6 Hz), 7.07 (tdd, 1H, J = 8.8, 2.6, 0.9 Hz), 4.80 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 3.83 (d, 1H, J = 14.1 Hz), 3.78 (d, 1H, J = 13.7 Hz), 3.68 (d, 1H, J = 13.7 Hz), 3.51 (d, 1H, J = 14.1 Hz), 2.77 (s, 3H), 2.16-2.03 (m, 2H), 1.67 (s, 3H), 1.22 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz), 0.69 (t, 3H, J = 7.3 Hz).

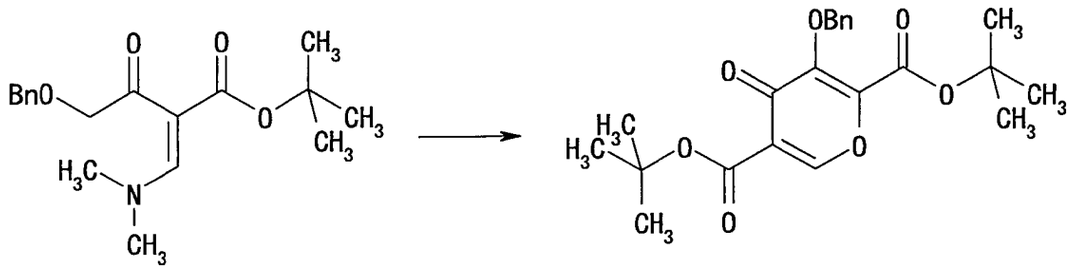
[0351]

Example 8

[0352]

step 8-1

[0353]



[0354]

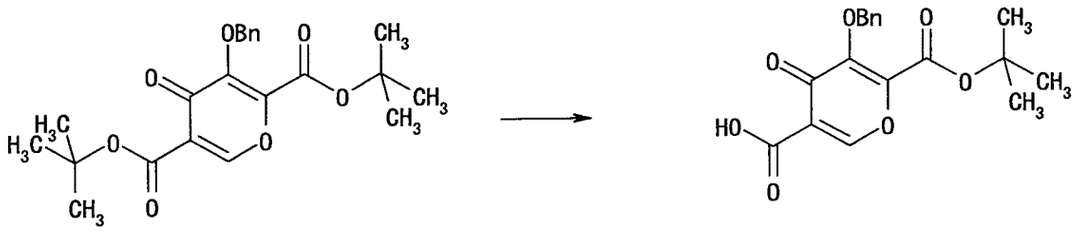
Under nitrogen, a solution of 1.6M lithium hexamethyldisilazide-THF (11.73 mL) in THF (100 mL) was cooled to -78°C, and a solution of the compound (5 g) obtained in step 2-2 in THF (15 mL) was added dropwise over 2 min under stirring. After stirring for 13 min, tert-butyl chloroglyoxylate (3.58 mL) was added at once. After stirring for 25 min, saturated aqueous potassium hydrogen sulfate solution and ethyl acetate were added, and the mixture was allowed to warm to room temperature. The organic layer was separated, washed with saturated aqueous potassium hydrogen sulfate solution and saturated brine, dried over sodium sulfate, and concentrated. Toluene was added to the residue, and the mixture was concentrated once. Toluene (100 mL) and triethylamine (10 mL) were added and the mixture was stirred at room temperature, and concentrated 30 min later. The above-mentioned operation was repeated once more, and the both were combined and purified by silica gel column chromatography (ethyl acetate:hexane=1:9 - 1:6) to give the object compound (4.496 g) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 8.37 (s, 1H), 7.52-7.49 (m, 2H), 7.39-7.29 (m, 3H), 5.27 (s, 2H), 1.57 (s, 9H), 1.51 (s, 9H).

[0355]

step 8-2

[0356]



[0357]

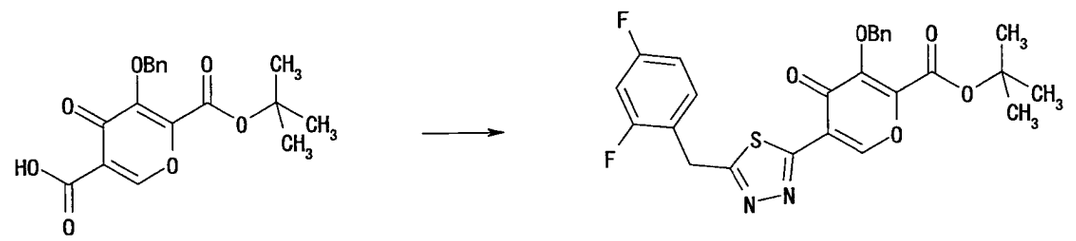
To a solution of the compound (4.49 g) obtained in step 8-1 in dioxane (5 mL) was added 4N hydrochloric acid/dioxane solution (20 mL) with stirring, and the mixture was stirred at room temperature for 20 min. The reaction mixture was concentrated, ethyl acetate/hexane (1:4) solution was added and the mixture was slurry washed. The residue was collected by filtration, and dried to give the object compound (3.30 g) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 8.78 (s, 1H), 7.48-7.44 (m, 2H), 7.41-7.34 (m, 3H), 5.34 (s, 2H), 1.54 (s, 9H).

[0358]

step 8-3

[0359]



[0360]

To a solution of the compound (1 g) obtained in step 8-2 in toluene (20 mL)/chloroform (5 mL) were added oxalyl chloride (0.326 mL) and dimethylformamide (0.01 mL) under stirring, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated, THF (20 mL) was added, and the mixture was cooled to -78°C under nitrogen. Triethylamine (1.21 mL) and (2,4-difluorophenyl)thioacetic acid hydrazide (555 mg) were added, and the temperature of the mixture was raised slowly. After 25 min, ethyl acetate and water were added, and the mixture was warmed to room

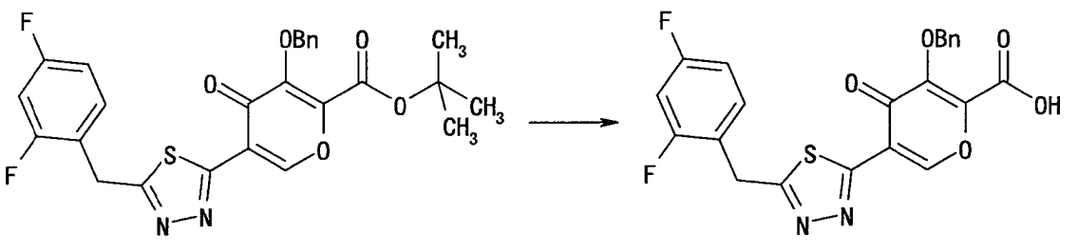
temperature. The mixture was extracted twice with ethyl acetate, and the organic layer was washed with saturated brine, dried over sodium sulfate, and concentrated. To the residue was added acetic acid (20 mL), and the mixture was stirred at 100°C for 2 hr. The mixture was allowed to cool to room temperature, and concentrated. The concentrate was purified by silica gel column chromatography (ethyl acetate:hexane=1:9 - 1:4) to give the object compound (112 mg) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 9.05 (s, 1H), 7.50-7.46 (m, 1H), 7.39-7.18 (m, 5H), 6.91-6.80 (m, 2H), 5.32 (s, 2H), 4.49 (s, 2H), 1.53 (s, 9H).

[0361]

step 8-4

[0362]



[0363]

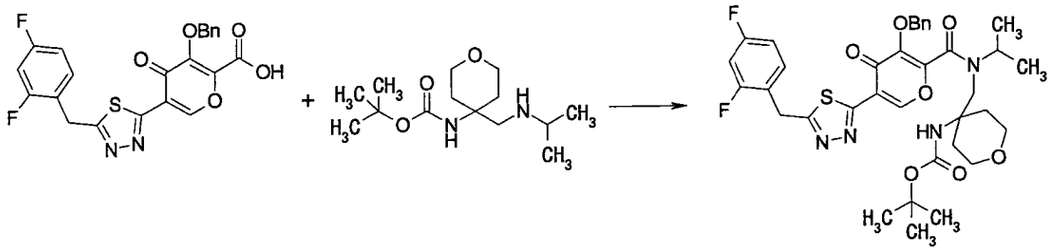
A solution of the compound (1.01 g) obtained in step 8-3 in formic acid (20 mL) was stirred at room temperature for 2 hr. The reaction mixture was concentrated, ethyl acetate/hexane (1:4) solution was added and the mixture was slurry washed. The crystals were collected by filtration. The mother liquor was concentrated, formic acid (20 mL) was added, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated, ethyl acetate/hexane (1:4) solution was added and the mixture was slurry washed. The crystals were collected by filtration. The both crystals were combined and dried to give the object compound (238 mg) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 9.13 (s, 1H), 7.43-7.18 (m, 6H), 6.93-6.79 (m, 2H), 5.67 (s, 2H), 4.51 (s, 2H).

[0364]

step 8-5

[0365]



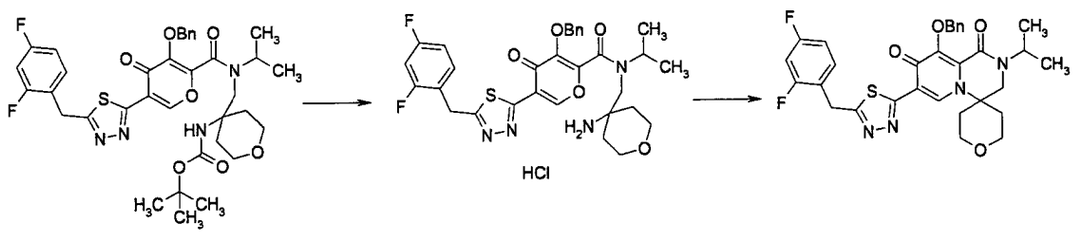
[0366]

To a solution of the compound (69 mg) obtained in step 8-4 in N,N-dimethylformamide (1.5 mL) were added O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (86 mg), 1-hydroxy-7-azabenzotriazole (HOAt) (31 mg), triethylamine (1.1 mL) and [4-(isopropylaminomethyl)tetrahydropyran-4-yl]carbamic acid tert-butyl ester (49 mg) under ice-cooling, and the mixture was stirred at room temperature overnight. To the reaction mixture was added 5% aqueous potassium hydrogen sulfate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution, dried, and concentrated. The concentrate was purified by silica gel thin layer chromatography (chloroform:methanol=10:1) to give the object compound (18 mg) described in the above-mentioned scheme.

[0367]

step 8-6

[0368]



[0369]

To the compound (18 mg) obtained in step 8-5 was added 4N

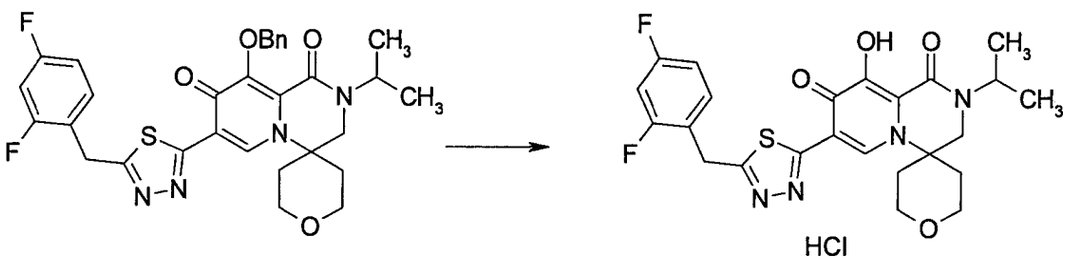
hydrochloric acid/dioxane solution (1 mL), and the mixture was left standing at room temperature for 1.5 hr. The reaction mixture was concentrated, 2-propanol (6 mL), water (0.6 mL) and saturated aqueous sodium hydrogen carbonate solution (0.6 mL) were added, and the mixture was stirred with heating at 100°C for 4 hr. The mixture was allowed to cool to room temperature once, left standing overnight, and stirred again with heating at 100°C for 8 hr. To the reaction mixture was added saturated brine, and the mixture was extracted with ethyl acetate, dried and concentrated. The concentrate was purified by silica gel thin layer chromatography (chloroform:methanol=10:1) to give the object compound (10 mg) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 9.05 (s, 1H), 7.66-7.62 (m, 2H), 7.38-7.28 (m, 4H), 6.88-6.81 (m, 2H), 5.38 (s, 2H), 4.97 (sep, 1H, J = 7.0 Hz), 4.47 (s, 2H), 4.11-4.04 (m, 2H), 3.74-3.65 (m, 2H), 3.55 (s, 2H), 2.45-2.36 (m, 2H), 2.01-1.94 (m, 2H), 1.22 (d, 6H, J = 7.0 Hz).

[0370]

step 8-7

[0371]



[0372]

The compound (10 mg) obtained in step 8-6 was dissolved in trifluoroacetic acid (1.0 mL), and the mixture was stood at room temperature for 50 min. Trifluoroacetic acid solution was concentrated, 4N hydrochloric acid/dioxane solution was added and the mixture was concentrated. Toluene was added and the mixture was concentrated. The obtained residue was crystallized from ethyl acetate (0.5 mL)-hexane (2 mL) to give

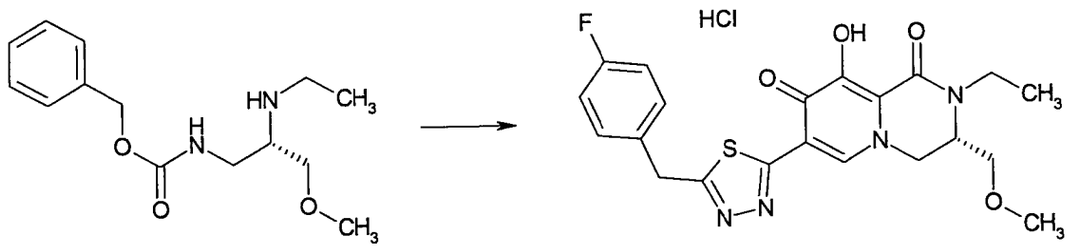
the object compound (4.7 mg) described in the above-mentioned scheme.

^{1}H-NMR (DMSO-d_6) δ: 13.25 (br s, 1H), 8.88 (s, 1H), 7.58-7.50 (m, 1H), 7.32-7.25 (m, 1H), 7.15-7.09 (m, 1H), 4.83 (sep, 1H, J = 6.9 Hz), 4.50 (s, 2H), 3.89-3.82 (m, 2H), 3.88 (br s, 2H), 3.80-3.73 (m, 2H), 2.31-2.22 (m, 2H), 2.01-1.94 (m, 2H), 1.23 (d, 6H, J = 6.9 Hz).

[0373]

Example 9

[0374]



[0375]

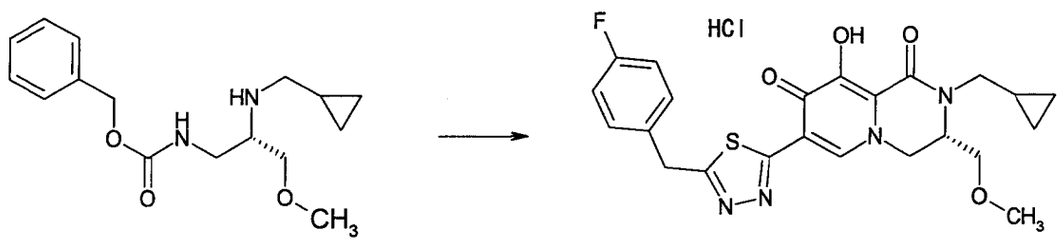
In the same manner as in step 2-9 (amino-protecting group was removed by a known method according to the protecting group) and step 2-11, the object compound (18.0 mg) described in the above-mentioned scheme was obtained from ((S)-2-ethylamino-3-methoxypropyl)carbamic acid benzyl ester (80 mg) obtainable from a commercially available compound by a known method.

^{1}H-NMR (DMSO-d_6) δ: 12.64-12.34 (m, 1H), 8.83 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.14 (m, 2H), 4.64 (dd, 1H, J = 13.4, 1.5 Hz), 4.47 (s, 2H), 4.42 (dd, 1H, J = 13.4, 4.4 Hz), 4.17-4.11 (m, 1H), 3.86 (dq, 1H, J = 14.0, 7.0 Hz), 3.54 (dd, 1H, J = 10.4, 4.9 Hz), 3.50 (dd, 1H, J = 10.4, 6.3 Hz), 3.27 (dq, 1H, J = 14.0, 7.0 Hz), 3.22 (s, 3H), 1.20 (t, 3H, J = 7.0 Hz).

[0376]

Example 10

[0377]



[0378]

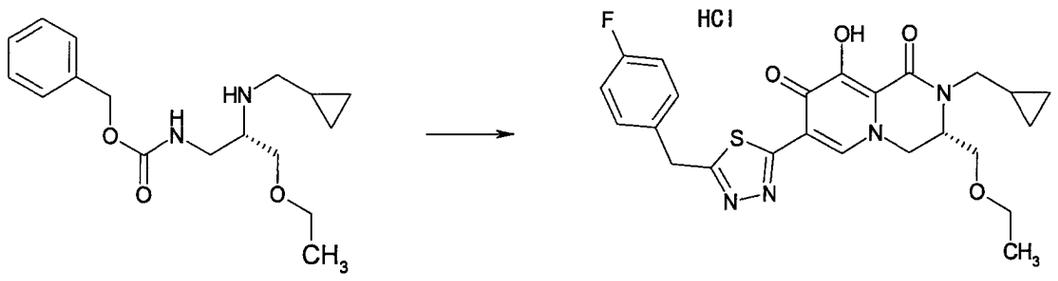
In the same manner as in step 2-9 (amino-protecting group was removed by a known method according to the protecting group) and step 2-11, the object compound (10.7 mg) described in the above-mentioned scheme was obtained from ((S)-2-cyclopropylmethylamino-3-methoxypropyl)carbamic acid benzyl ester (36 mg) obtainable from a commercially available compound by a known method.

^{1}H-NMR (DMSO-d_6) δ: 12.46 (br s, 1H), 8.85 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.67 (dd, 1H, J = 13.7, 1.6 Hz), 4.47 (s, 2H), 4.45 (dd, 1H, J = 13.7, 3.9 Hz), 4.27-4.20 (m, 1H), 3.69 (dd, 1H, J = 14.0, 7.0 Hz), 3.58 (dd, 1H, J = 10.3, 4.8 Hz), 3.51 (dd, 1H, J = 10.3, 6.5 Hz), 3.21 (dd, 1H, J = 14.0, 7.0 Hz), 3.21 (s, 3H), 1.21-1.10 (m, 1H), 0.59-0.47 (m, 2H), 0.44-0.36 (m, 1H), 0.36-0.27 (m, 1H).

[0379]

Example 11

[0380]



[0381]

In the same manner as in step 2-9 (amino-protecting group was removed by a known method according to the protecting group) and step 2-11, the object compound (32.0 mg) described in the above-mentioned scheme was obtained from ((S)-2-cyclopropylmethylamino-3-ethoxypropyl)carbamic acid benzyl

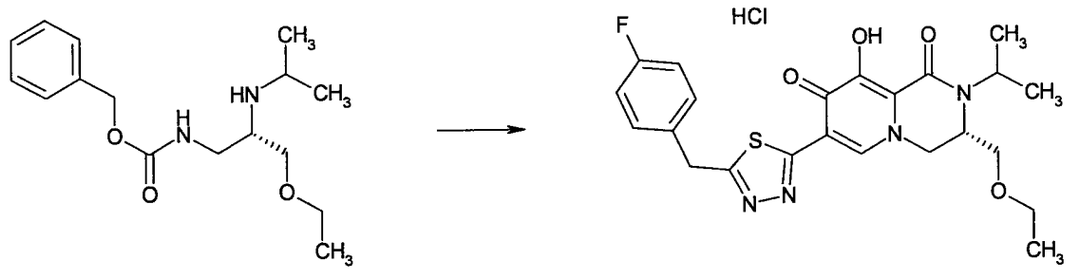
ester (295 mg) obtainable from a commercially available compound by a known method.

^{1}H-NMR (DMSO-d_6) δ: 12.50 (br s, 1H), 8.84 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.15 (m, 2H), 4.67 (d, 1H, J=12.3 Hz), 4.46 (s, 2H), 4.46-4.42 (m, 1H), 4.22-4.19 (m, 2H), 3.67 (dd, 1H, J=14.2, 7.2 Hz), 3.61 (dd, 1H, J=10.4, 4.4 Hz), 3.55 (dd, 1H, J=10.4, 6.2 Hz), 3.40-3.32 (m, 2H), 3.21 (dd, 1H, J=14.2, 7.0 Hz), 0.94 (t, 3H, J=7.0 Hz), 0.54-0.46 (m, 2H), 0.41-0.37 (m, 1H), 0.33-0.27 (m, 1H).

[0382]

Example 12

[0383]



[0384]

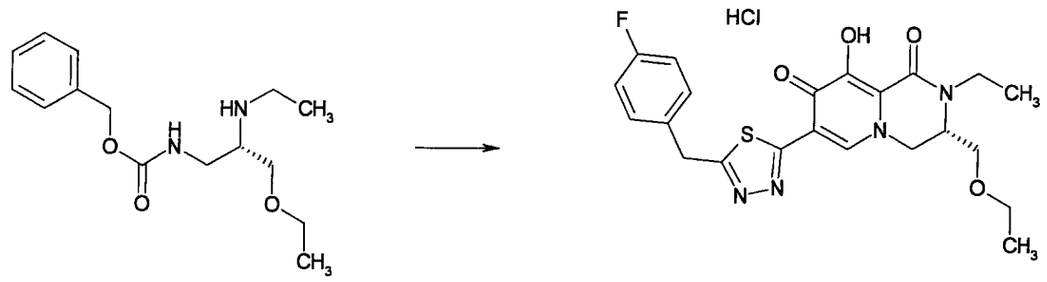
In the same manner as in step 2-9 (amino-protecting group was removed by a known method according to the protecting group) and step 2-11, the object compound (35.0 mg) described in the above-mentioned scheme was obtained from ((S)-3-ethoxy-2-isopropylaminopropyl)carbamic acid benzyl ester (230 mg) obtainable from a commercially available compound by a known method.

^{1}H-NMR (DMSO-d_6) δ: 12.40 (br s, 1H), 8.85 (s, 1H), 7.43-7.40 (m, 2H), 7.22-7.16 (m, 2H), 4.67, (d, 1H, J=11.9 Hz), 4.51-4.47 (m, 1H), 4.47 (s, 2H), 4.35 (dd, 1H, J=13.3, 3.9 Hz), 4.20-4.16 (m, 1H), 3.54 (dd, 1H, J=10.5, 4.1 Hz), 3.45-3.32 (m, 3H), 1.30 (d, 3H, J=4.6 Hz), 1.28 (d, 3H, J=4.6 Hz), 0.96 (t, 3H, J=7.0 Hz).

[0385]

Example 13

[0386]



[0387]

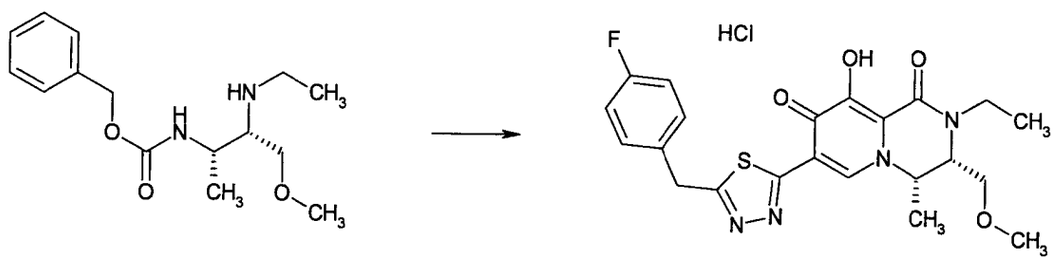
In the same manner as in step 2-9 (amino-protecting group was removed by a known method according to the protecting group) and step 2-11, the object compound (37.0 mg) described in the above-mentioned scheme was obtained from ((S)-3-ethoxy-2-ethylaminopropyl)carbamic acid benzyl ester (250 mg) obtainable from a commercially available compound by a known method.

^{1}H-NMR (DMSO-d_6) δ: 12.50 (br s, 1H), 8.84 (s, 1H), 7.43-7.40 (m, 2H), 7.22-7.16 (m, 2H), 4.67, (dd, 1H, J=13.5, 1.5 Hz), 4.47 (s, 2H), 4.35 (dd, 1H, J=13.5, 4.2 Hz), 4.14-4.11 (m, 1H), 3.91-3.82 (m, 1H), 3.60-3.53 (m, 2H), 3.41-3.34 (m, 2H), 3.31-3.23 (m, 1H), 1.20 (t, 3H, J=7.2 Hz), 0.96 (t, 3H, J=7.0Hz).

[0388]

Example 14

[0389]



[0390]

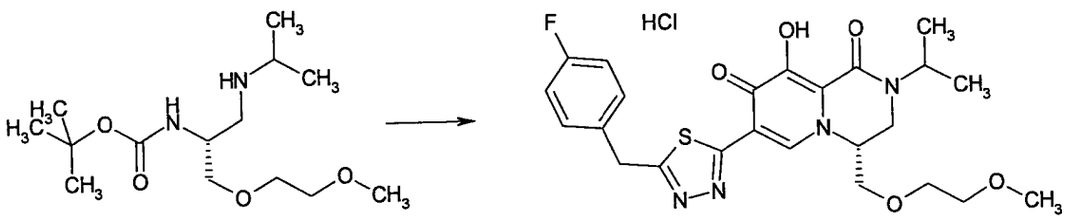
In the same manner as in step 2-9 (amino-protecting group was removed by a known method according to the protecting group) and step 2-11, the object compound (32.9 mg) described in the above-mentioned scheme was obtained from ((1S,2S)-2-ethylamino-3-methoxy-1-methylpropyl)carbamic acid benzyl ester (51 mg) obtainable from a commercially available compound by a known method.

^{1}H-NMR (DMSO-d_6) δ: 12.77 (br s, 1H), 8.62 (s, 1H), 7.42-7.38 (m, 2H), 7.20-7.16 (m, 2H), 4.77-4.71 (m, 1H), 4.47 (s, 2H), 4.14 (q, 1H, J=4.0 Hz), 3.92-3.84 (m, 1H), 3.59 (d, 2H, J=4.4 Hz), 3.33-3.26 (m, 1H), 3.18 (s, 3H), 1.64 (d, 3H, J=6.5 Hz), 1.21 (t, 3H, J=7.1 Hz).

[0391]

Example 15

[0392]



[0393]

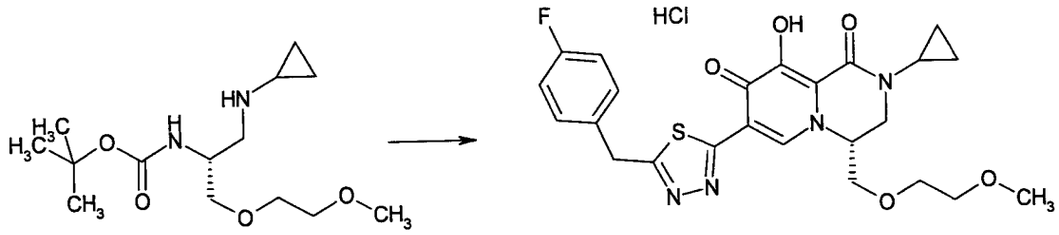
In the same manner as in step 2-9 and step 2-11, the object compound (6.2 mg) described in the above-mentioned scheme was obtained from [(R)-2-isopropylamino-1-((2-methoxyethoxy)methyl)ethyl]carbamic acid tert-butyl ester (19.3 mg) obtainable from a commercially available compound by a known method.

^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.82 (s, 1H), 7.45-7.38 (m, 2H), 7.23-7.15 (m, 2H), 4.99-4.91 (m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 3.84 (dd, 1H, J = 13.8, 4.1 Hz), 3.78-3.68 (m, 2H), 3.64 (dd, 1H, J = 10.4, 7.7 Hz), 3.58-3.45 (m, 2H), 3.34 (t, 2H, J = 4.5 Hz), 3.11 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).

[0394]

Example 16

[0395]



[0396]

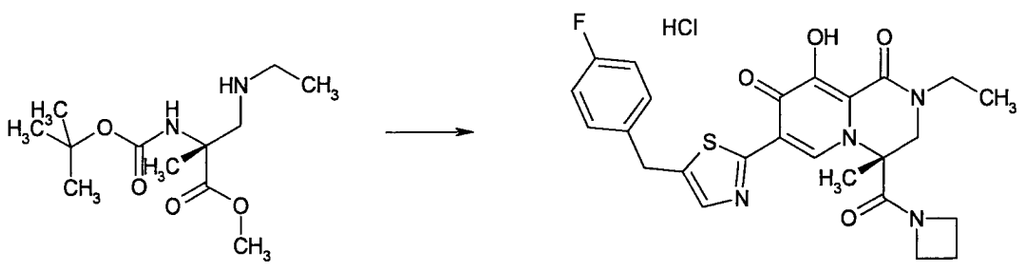
In the same manner as in step 2-9 and step 2-11, the object compound (10.7 mg) described in the above-mentioned scheme was obtained from [(R)-2-cyclopropylamino-1-((2-methoxyethoxy)methyl)ethyl]carbamic acid tert-butyl ester (16 mg) obtainable from a commercially available compound by a known method.

^{1}H-NMR (DMSO-d_6) δ: 8.81 (s, 1H), 7.45-7.37 (m, 2H), 7.22-7.14 (m, 2H), 4.92-4.84 (br m, 1H), 4.47 (s, 2H), 4.09-3.99 (m, 1H), 3.74-3.57 (m, 3H), 3.56-3.44 (m, 2H), 3.34 (t, 2H, J = 4.6 Hz), 3.13 (s, 3H), 2.94-2.84 (m, 1H), 0.97-0.67 (m, 4H).

[0397]

Example 17

[0398]



[0399]

In the same manner as in step 2-9 to step 2-11, the object compound (39 mg) described in the above-mentioned scheme was obtained from (R)-2-tert-butoxycarbonylamino-3-ethylamino-2-methylpropionic acid methyl ester (60 mg) obtainable from a commercially available compound by a known method.

^{1}H-NMR (DMSO-d_6) δ: 12.69 (m, 1H), 8.60 (s, 1H), 7.69 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.12 (m, 2H), 4.20 (s, 2H), 4.18-4.13 (m, 1H), 4.01 (d, 1H, J=13.5 Hz), 3.89 (d, 1H, J=13.5 Hz), 3.87-3.80 (m, 2H), 3.67-3.61 (m, 1H), 3.54-3.44 (m, 2H), 2.12-2.04 (m, 2H), 1.91 (s, 3H), 1.10 (t, 3H, J=7.2 Hz).

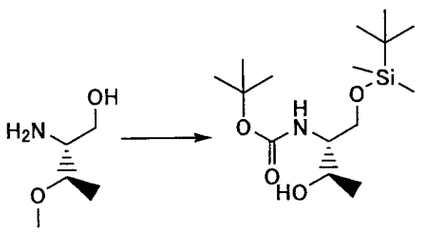
[0400]

Example 340

[0401]

step 340-1

[0402]



[0403]

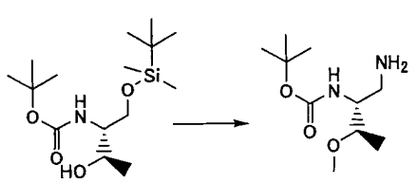
To a solution of L-threoninol (2.05 g) in chloroform (14 mL) were added di-tert-butyl dicarbonate (4.26 g) and saturated aqueous sodium hydrogen carbonate solution (10 mL) and the mixture was stirred at room temperature for 3 hr and left standing for 3 days. To the reaction mixture was added saturated brine, and the mixture was extracted with chloroform. The organic layer was dried, and concentrated. The obtained residue was dissolved in dimethylformamide (40 mL) and, under ice-cooling, imidazole (2.97 g) and tert-butylchlorodimethylsilane (1.49 g) were added, and the mixture was stirred at room temperature for 45 min. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried, and concentrated. The concentrate was purified by silica gel column chromatography (ethyl acetate:hexane=1:10 - 1:3) to give the object compound (2.39 g) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 5.18 (d, 1H, J = 8.2 Hz), 4.18-4.14 (m, 1H), 3.89 (dd, 1H, J = 10.4, 3.3 Hz), 3.82 (dd, 1H, J = 10.4, 2.6 Hz), 3.48-3.45 (m, 1H), 3.29 (s, 1H), 1.46 (s, 9H), 1.18 (d, 3H, J = 6.2 Hz), 0.90 (s, 9H), 0.08 (s, 6H).

[0404]

step 340-2

[0405]



[0406]

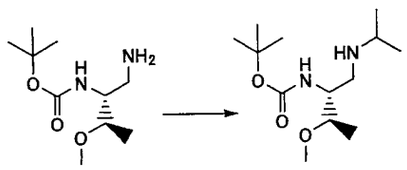
To a solution of the compound (2.39 g) obtained in step 340-1 in toluene (12 mL) were added tetrabutylammonium hydrogen sulfate (76 mg), 50% aqueous sodium hydroxide solution (8 mL) and methyl sulfate (922 μL) under ice-cooling, and the mixture was stirred at room temperature for 90 min. Ice water was added, and the mixture was extracted with toluene. The organic layer was washed with saturated brine, dried, and concentrated. The obtained residue was dissolved in tetrahydrofuran (20 mL), 1.0M tetrabutylammonium fluoride/tetrahydrofuran solution (8.16 mL) was added and the mixture was stirred at room temperature for 100 min. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and concentrated. Toluene was added and the mixture was concentrated again. To a solution of the obtained residue in tetrahydrofuran (40 mL) were added phthalimide (1.85 g) and triphenylphosphine (3.30 g), 2.2M diethyl azodicarboxylate/toluene solution (5.05 mL) was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 90 min. The reaction mixture was concentrated, and the concentrate was purified by silica gel column chromatography (ethyl acetate:hexane=1:10 - 1:2). The obtained solid was dissolved in ethanol (60 mL)-toluene (60 mL), hydrazine monohydrate (2.05 mL) was added, and the mixture was stirred at 80°C for 4 hr. The mixture was allowed to cool to room temperature, the solid was filtered off, and the filtrate was concentrated. Toluene was added to the residue, and the precipitated solid was filtered off. The filtrate was concentrated to give the object compound (1.54 g) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 4.82 (br s, 1H), 3.52-3.45 (m, 2H), 3.31 (s, 3H), 2.81 (dd, 2H, J = 13.0, 6.0 Hz), 2.76 (dd, 2H, J = 13.0, 7.1 Hz), 1.51 (br s, 2H), 1.15 (d, 3H, J = 6.2 Hz).

[0407]

step 340-3

[0408]



[0409]

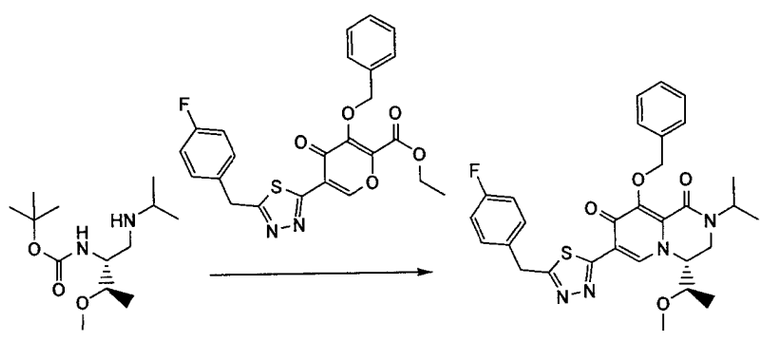
To a solution of the compound (187 mg) obtained in step 340-2 in chloroform (3 mL) were added acetone (76 μL), acetic acid (59 μL) and sodium triacetoxyborohydride (218 mg) under ice-cooling, and the mixture was stirred at room temperature for 5 hr. The reaction mixture was diluted with chloroform, saturated aqueous sodium hydrogen carbonate solution was added and the mixture was stirred. The chloroform layer was dried and concentrated to give the object compound (190 mg) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 4.84 (br s, 1H), 3.59-3.50 (m, 2H), 3.32 (s, 3H), 2.83-2.66 (m, 3H), 1.51 (br s, 1H), 1.14 (d, 3H, J = 6.4 Hz), 1.04 (d, 3H, J = 6.4 Hz), 1.04 (d, 3H, J = 6.4 Hz).

[0410]

step 340-4

[0411]



[0412]

The compound (190 mg) obtained in step 340-3 was dissolved in trifluoroacetic acid (2.0 mL), and the mixture was stood at room temperature for 20 min. Trifluoroacetic acid solution was concentrated, tetrahydrofuran (1.58 mL) and diisopropylethylamine (636 μL) were added to give a solution.

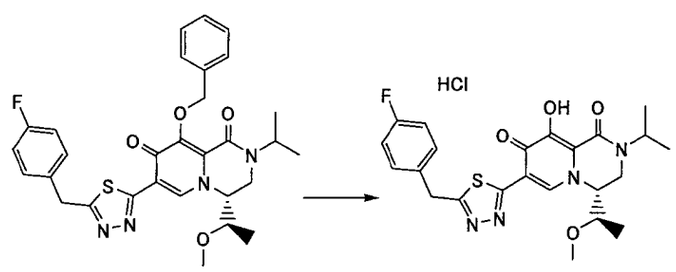
To a solution of the compound (75 mg) obtained in step 2-5 in tetrahydrofuran (500 μL) was added the above-mentioned solution (634 μL), and the mixture was stirred at room temperature for 15 min. Toluene (6 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (250 μL) were added and the mixture was stirred at 100°C for 20 min. Acetic acid (750 μL) was added and the mixture was stirred at 100°C for 1 hr. The reaction mixture was allowed to cool to room temperature, 5% aqueous potassium hydrogen sulfate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried, and concentrated. The concentrate was purified by silica gel thin layer chromatography (ethyl acetate:methanol=15:1) to give the object compound (73 mg) described in the above-mentioned scheme.

^{1}H-NMR ($CDCl_3$) δ: 8.65 (s, 1H), 7.65-7.62 (m, 2H), 7.35-7.25 (m, 5H), 7.04-6.98 (m, 2H), 5.51 (d, 1H, J = 9.9 Hz), 5.24 (d, 1H, J = 9.9 Hz), 4.94 (sep, 1H, J = 6.8 Hz), 4.43 (s, 2H), 3.93-3.89 (m, 1H), 3.67 (dd, 1H, J = 14.2, 3.9 Hz), 3.47 (dq, 1H, J = 8.8, 6.0 Hz), 3.42 (dd, 1H, J = 14.2, 1.5 Hz), 3.15 (s, 3H), 1.29 (d, 3H, J = 6.0 Hz), 1.19 (d, 3H, J = 6.8 Hz), 1.14 (d, 3H, J = 6.8 Hz).

[0413]

step 340-5

[0414]



[0415]

The compound (72 mg) obtained in step 340-4 was dissolved in trifluoroacetic acid (1.0 mL), and the mixture was stood at room temperature for 4 hr. Trifluoroacetic acid solution was

concentrated, toluene was added and the mixture was concentrated. Ethyl acetate, 4N hydrochloric acid/ethyl acetate solution, and hexane were added to allow crystallization to give the object compound (65 mg) described in the above-mentioned scheme.

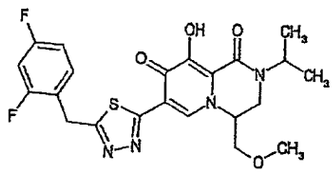
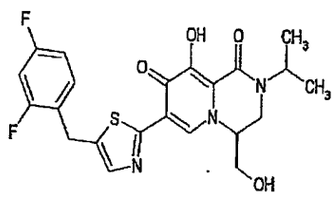
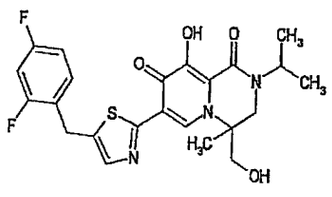
^{1}H-NMR (DMSO-D_6) δ: 12.82 (br s, 1H), 8.72 (s, 1H), 7.44-7.41 (m, 2H), 7.21-7.17 (m, 2H), 4.77 (sep, 1H, J = 6.6 Hz), 4.65 (ddd, 1H, J = 8.2, 4.1, 0.9 Hz), 4.47 (s, 2H), 3.88 (dd, 1H, J = 14.0, 4.1 Hz), 3.76 (dd, 1H, J = 14.0, 0.9 Hz), 3.52 (dq, 1H, J = 8.2, 6.2 Hz), 3.03 (s, 3H), 1.21 (d, 3H, J = 6.2 Hz), 1.20 (d, 3H, J = 6.6 Hz), 1.17 (d, 3H, J = 6.6 Hz).

[0416]

The compounds of Examples 18 to 465 shown in the following Tables were produced in the same manner as in the above-mentioned Examples 1 to 17 and 340, or by using other conventional methods where necessary. The structural formulas and property data of the compounds of Examples 18 to 465 are shown in the following Tables.

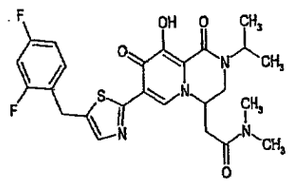
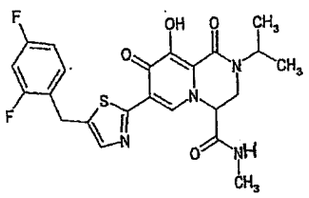
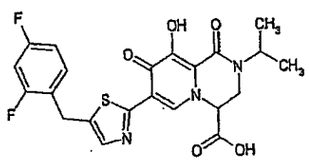
[0417]

[Table 1-1]

No.	structural formula	salt	^{1}H-NMR
18		—	^{1}H-NMR (DMSO-d_6) δ: 12.82 (s, 1H), 8.80 (s, 1H), 7.54 (td, 1H, J = 8.8, 6.7 Hz), 7.29 (ddd, 1H, J = 10.2, 9.3, 2.6 Hz), 7.12 (tdd, 1H, J = 8.8, 2.6 0.9 Hz), 5.01-4.93 (br m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 3.84 (dd, 1H, J = 13.9, 3.9 Hz), 3.75 (dd, 1H, J = 13.9, 1.4 Hz), 3.62 (dd, 1H, J = 10.2, 5.8 Hz), 3.57 (dd, 1H, J = 10.2, 7.7 Hz), 3.25 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
19		—	^{1}H-NMR (DMSO-d_6) δ: 12.69 (br s, 1H), 8.58 (s, 1H), 7.64 (s, 1H), 7.45 (td, 1H, J = 8.8, 6.8 Hz), 7.24 (ddd, 1H, J = 10.6, 9.7, 2.9 Hz), 7.07 (tdd, 1H, J = 8.8, 2.9, 1.0 Hz), 4.75 (sep, 1H, J = 6.6 Hz), 4.69-4.59 (br m, 1H), 4.21 (s, 2H), 3.81 (dd, 1H, J = 13.5, 3.7 Hz), 3.72 (dd, 1H, J = 13.5, 1.5 Hz), 3.67 (dd, 1H, J = 11.7, 5.3 Hz), 3.53 (dd, 1H, J = 11.7, 8.6 Hz), 1.16 (d, 3H, J = 6.6 Hz), 1.15 (d, 3H, J = 6.6 Hz).
20		—	^{1}H-NMR (DMSO-d_6) δ: 13.11 (br s, 1H), 8.60 (s, 1H), 7.66 (s, 1H), 7.44 (td, 1H, J = 8.7, 6.7 Hz), 7.24 (ddd, 1H, J = 10.4, 9.3, 2.8 Hz), 7.07 (tdd, 1H, J = 8.7, 2.8, 0.9 Hz), 4.79 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 3.89 (d, 1H, J = 14.1 Hz), 3.79 (d, 1H, J = 14.1 Hz), 3.72 (d, 1H, J = 13.7 Hz), 3.63 (d, 1H, J = 13.7 Hz), 1.58 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz).

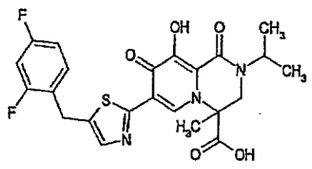
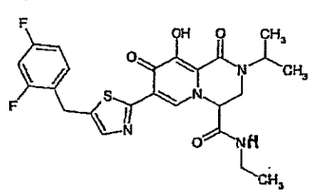
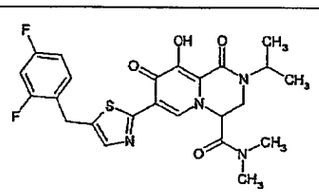
[0418]

[Table 1-2]

No.	structural formula	salt	^{1}H-NMR
21		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.67 (s, 1H), 8.71 (s, 1H), 7.65 (s, 1H), 7.49–7.41 (m, 1H), 7.33–7.20 (m, 1H), 7.11–7.02 (m, 1H), 5.11–5.02 (m, 1H), 4.84–4.73 (m, 1H), 4.21 (s, 2H), 3.87–3.73 (m, 2H), 2.89–2.82 (m, 2H), 2.86 (s, 3H), 2.79 (s, 3H), 1.13 (d, 3H, J = 7.0 Hz), 1.13 (d, 3H, J = 6.7 Hz).
22		—	^{1}H-NMR (DMSO-d_6) δ : 12.37 (s, 1H), 8.66 (s, 1H), 8.25 (q, 1H, J = 4.4 Hz), 7.64 (s, 1H), 7.45 (td, 1H, J = 8.6, 6.5 Hz), 7.25 (ddd, 1H, J = 10.4, 9.5, 2.8 Hz), 7.07 (tdd, 1H, J = 8.6, 2.8, 0.9 Hz), 5.52–5.46 (br m, 1H), 4.69 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.02 (dd, 1H, J = 13.9, 2.1 Hz), 3.94 (dd, 1H, J = 13.9, 3.5 Hz), 2.61 (d, 3H, J = 4.4 Hz), 1.12 (d, 3H, J = 6.7 Hz), 1.03 (d, 3H, J = 6.7 Hz).
23		—	^{1}H-NMR (DMSO-d_6) δ : 12.42 (br s, 1H), 8.75 (s, 1H), 7.65 (s, 1H), 7.46 (td, 1H, J = 8.8, 7.1 Hz), 7.24 (ddd, 1H, J = 10.6, 9.7, 2.4 Hz), 7.07 (tdd, 1H, J = 8.8, 2.4, 0.9 Hz), 5.71–5.66 (br m, 1H), 4.73 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.03 (dd, 1H, J = 13.5, 2.6 Hz), 3.95 (dd, 1H, J = 13.5, 4.0 Hz), 1.16 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz).

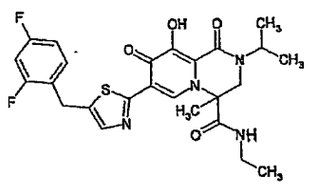
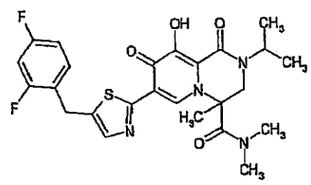
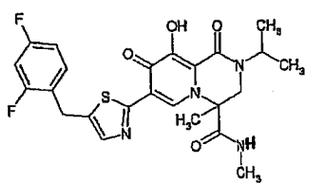
[0419]

[Table 1-3]

No.	structural formula	salt	^{1}H-NMR
24		—	^{1}H-NMR (DMSO-d_6) δ : 12.90 (br s, 1H), 8.59 (s, 1H), 7.66 (s, 1H), 7.44 (td, 1H, J = 9.0, 7.3 Hz), 7.24 (ddd, 1H, J = 10.8, 9.3, 2.4 Hz), 7.07 (tdd, 1H, J = 9.0, 2.4, 1.0 Hz), 4.72 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.05 (d, 2H, J = 13.2 Hz), 3.74 (d, 1H, J = 13.2 Hz), 1.92 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.14 (d, 3H, J = 6.7 Hz).
25		—	^{1}H-NMR (DMSO-d_6) δ : 12.39 (s, 1H), 8.66 (s, 1H), 8.36 (t, 1H, J = 5.4 Hz), 7.64 (s, 1H), 7.45 (td, 1H, J = 8.7, 6.6 Hz), 7.25 (ddd, 1H, J = 10.4, 9.3, 2.6 Hz), 7.07 (tdd, 1H, J = 8.7, 2.6, 0.9 Hz), 5.50–5.43 (br m, 1H), 4.70 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.03 (dd, 1H, J = 13.9, 1.6 Hz), 3.95 (dd, 1H, J = 13.9, 3.7 Hz), 3.09 (qd, 2H, J = 7.4, 5.4 Hz), 1.13 (d, 3H, J = 6.7 Hz), 1.05 (d, 3H, J = 6.7 Hz), 1.02 (t, 3H, J = 7.4 Hz).
26		—	^{1}H-NMR (DMSO-d_6) δ : 12.32 (br s, 1H), 8.71 (s, 1H), 7.63 (s, 1H), 7.46 (td, 1H, J = 8.7, 6.6 Hz), 7.25 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.07 (tdd, 1H, J = 8.7, 2.6, 1.2 Hz), 6.05–6.00 (br m, 1H), 4.71 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 3.98 (dd, 1H, J = 14.4, 3.9 Hz), 3.80 (dd, 1H, J = 14.4, 1.4 Hz), 3.17 (s, 3H), 2.82 (s, 3H), 1.14 (d, 3H, J = 6.7 Hz), 0.98 (d, 3H, J = 6.7 Hz).

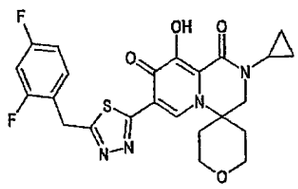
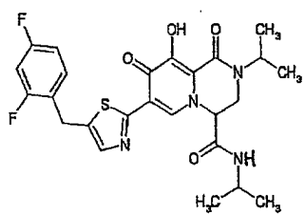
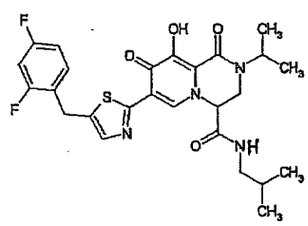
[0420]

[Table 1-4]

No.	structural formula	salt	^{1}H-NMR
27		—	^{1}H-NMR (DMSO-d_6) δ : 12.80 (s, 1H), 8.50 (s, 1H), 8.13 (t, 1H, J = 5.4 Hz), 7.66 (s, 1H), 7.44 (td, 1H, J = 8.7, 6.7 Hz), 7.24 (ddd, 1H, J = 10.4, 9.3, 2.7 Hz), 7.07 (tdd, 1H, J = 8.7, 2.7, 0.9 Hz), 4.71 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.08 (d, 1H, J = 13.8 Hz), 3.78 (d, 1H, J = 13.8 Hz), 3.17–2.98 (m, 2H), 1.92 (s, 3H), 1.15 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz), 1.00 (t, 3H, J = 7.2 Hz).
28		—	^{1}H-NMR (DMSO-d_6) δ : 12.85 (s, 1H), 8.42 (s, 1H), 7.66 (s, 1H), 7.45 (td, 1H, J = 8.7, 6.7 Hz), 7.24 (ddd, 1H, J = 10.4, 9.7, 2.8 Hz), 7.07 (tdd, 1H, J = 8.7, 2.8, 0.9 Hz), 4.73 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.12 (d, 1H, J = 14.1 Hz), 3.79 (d, 1H, J = 14.1 Hz), 2.93 (br s, 6H), 1.97 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz).
29		—	^{1}H-NMR (DMSO-d_6) δ : 12.78 (s, 1H), 8.51 (s, 1H), 8.05 (q, 1H, J = 4.2 Hz), 7.66 (s, 1H), 7.44 (td, 1H, J = 8.7, 6.6 Hz), 7.24 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.07 (tdd, 1H, J = 8.7, 2.6, 0.9 Hz), 4.70 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.05 (d, 1H, J = 13.7 Hz), 3.78 (d, 1H, J = 13.7 Hz), 2.59 (d, 3H, J = 4.2 Hz), 1.92 (s, 3H), 1.14 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.7 Hz).

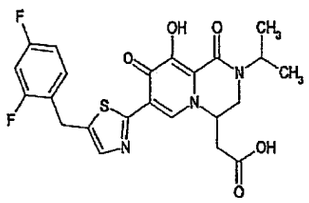
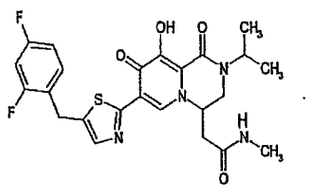
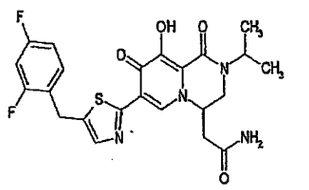
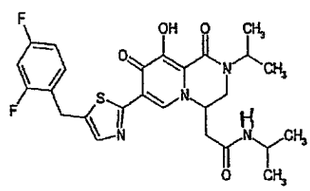
[0421]

[Table 1-5]

No.	structural formula	salt	^{1}H-NMR
30		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.17 (br s, 1H), 8.87 (s, 1H), 7.54 (td, 1H, J = 8.5, 6.9 Hz), 7.29 (ddd, 1H, J = 10.5, 9.3, 2.4 Hz), 7.11 (tdd, 1H, J = 8.5, 2.4, 1.2 Hz), 4.49 (s, 2H), 3.90 (s, 2H), 3.88–3.81 (m, 2H), 3.74–3.66 (m, 2H), 2.98 (ddt, 1H, J = 7.3, 6.9, 4.0 Hz), 2.28–2.19 (m, 2H), 1.98–1.91 (m, 2H), 0.93–0.80 (m, 4H).
31		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.42 (br s, 1H), 8.65 (s, 1H), 8.30 (d, 1H, J = 7.4 Hz), 7.64 (s, 1H), 7.45 (td, 1H, J = 8.6, 6.5 Hz), 7.25 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.07 (tdd, 1H, J = 8.6, 2.6, 0.9 Hz), 5.46–5.41 (br m, 1H), 4.71 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.03 (dd, 1H, J = 14.0, 1.9 Hz), 3.95 (dd, 1H, J = 14.0, 3.6 Hz), 3.85–3.74 (m, 1H), 1.13 (d, 3H, J = 6.7 Hz), 1.09 (d, 3H, J = 6.7 Hz), 1.07 (d, 3H, J = 7.0 Hz), 1.05 (d, 3H, J = 7.0 Hz).
32		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.40 (br s, 1H), 8.68 (s, 1H), 8.31 (dd, 1H, J = 6.2, 5.7 Hz), 7.64 (s, 1H), 7.45 (td, 1H, J = 8.7, 6.6 Hz), 7.24 (ddd, 1H, J = 10.4, 9.3, 2.8 Hz), 7.07 (tdd, 1H, J = 8.7, 2.8, 1.2 Hz), 5.51–5.46 (br m, 1H), 4.68 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.04 (dd, 1H, J = 14.1, 2.1 Hz), 3.94 (dd, 1H, J = 14.1, 3.6 Hz), 2.97 (ddd, 1H, J = 12.8, 6.6, 6.2 Hz), 2.78 (ddd, 1H, J = 12.8, 6.6, 5.7 Hz), 1.67 (sep, 1H, J = 6.5 Hz), 1.12 (d, 3H, J = 6.7 Hz), 1.04 (d, 3H, J = 6.7 Hz), 0.83 (d, 3H, J = 6.5 Hz), 0.82 (d, 3H, J = 6.5 Hz).

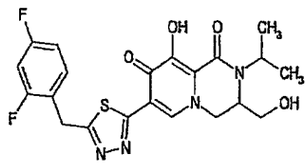
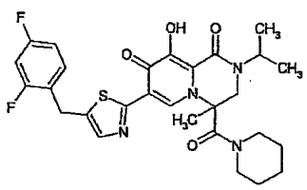
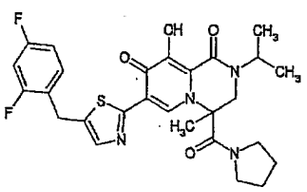
[0422]

[Table 1-6]

No.	structural formula	salt	^{1}H-NMR
33		—	^{1}H-NMR (DMSO-d_6) δ: 8.69 (s, 1H), 7.65 (s, 1H), 7.50–7.40 (m, 1H), 7.33–7.20 (m, 1H), 7.11–7.03 (m, 1H), 5.16–5.04 (m, 1H), 4.84–4.71 (m, 1H), 4.21 (s, 2H), 3.89–3.68 (m, 2H), 2.92–2.64 (m, 2H), 1.15 (t, 6H, J = 6.3 Hz).
34		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.64 (br s, 1H), 8.54 (s, 1H), 7.95–7.87 (m, 1H), 7.64 (s, 1H), 7.50–7.41 (m, 1H), 7.33–7.20 (m, 1H), 7.12–7.03 (m, 1H), 5.08–4.99 (m, 1H), 4.84–4.74 (m, 1H), 4.21 (s, 2H), 3.88–3.65 (m, 2H), 2.70–2.54 (m, 2H), 2.45 (d, 3H, J = 4.4 Hz), 1.17 (d, 3H, J = 6.5 Hz), 1.14 (d, 3H, J = 7.2 Hz).
35		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.58 (s, 1H), 7.65 (s, 1H), 7.49–7.38 (m, 2H), 7.28–7.19 (m, 1H), 7.11–7.03 (m, 1H), 7.00 (br s, 1H), 5.07–4.97 (m, 1H), 4.85–4.73 (m, 1H), 4.21 (s, 2H), 3.91–3.65 (m, 2H), 2.71–2.51 (m, 2H), 1.18 (d, 3H, J = 7.0 Hz), 1.15 (d, 3H, J = 7.2 Hz).
36		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.68 (br s, 1H), 8.46 (s, 1H), 7.85 (d, 1H, J = 7.7 Hz), 7.63 (s, 1H), 7.48–7.39 (m, 1H), 7.29–7.19 (m, 1H), 7.12–7.03 (m, 1H), 5.05–4.94 (m, 1H), 4.86–4.74 (m, 1H), 4.20 (s, 2H), 3.88–3.60 (m, 3H), 2.70–2.46 (m, 2H), 1.18 (d, 3H, J = 7.0 Hz), 1.15 (d, 3H, J = 7.2 Hz), 0.92 (d, 3H, J = 6.7 Hz), 0.69 (d, 3H, J = 6.7 Hz).

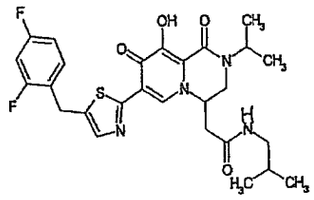
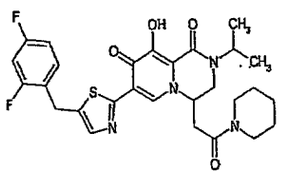
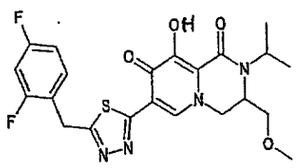
[0423]

[Table 1-7]

No.	structural formula	salt	^{1}H-NMR
37		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.80 (s, 1H), 7.57–7.49 (m, 1H), 7.32–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.67 (dd, 1H, J = 13.2, 1.4 Hz), 4.51 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.34 (dd, 1H, J = 13.2, 3.5 Hz), 4.00–3.93 (m, 1H), 3.57 (dd, 1H, J = 11.5, 3.5 Hz), 3.36 (dd, 1H, J = 11.5, 8.1 Hz), 1.29 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).
38		—	^{1}H-NMR (DMSO-d_6) δ: 12.97 (br s, 1H), 8.38 (s, 1H), 7.67 (s, 1H), 7.45 (td, 1H, J = 8.8, 6.6 Hz), 7.25 (ddd, 1H, J = 10.2, 9.3, 2.6 Hz), 7.07 (tdd, 1H, J = 8.8, 2.6, 0.9 Hz), 4.75 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.03 (d, 1H, J = 13.9 Hz), 3.80 (d, 1H, J = 13.9 Hz), 3.56–3.35 (br m, 4H), 1.90 (s, 3H), 1.59–1.50 (br m, 2H), 1.49–1.40 (br m, 4H), 1.18 (d, 3H, J = 6.7 Hz), 1.14 (d, 3H, J = 6.7 Hz).
39		—	^{1}H-NMR (DMSO-d_6) δ: 12.79 (br s, 1H), 8.52 (s, 1H), 7.66 (s, 1H), 7.45 (td, 1H, J = 8.8, 6.6 Hz), 7.24 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.07 (tdd, 1H, J = 8.8, 2.6, 0.9 Hz), 4.70 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.11 (d, 1H, J = 13.9 Hz), 3.74 (d, 1H, J = 13.9 Hz), 3.64–3.54 (br m, 1H), 3.42–3.32 (br m, 1H), 3.32–3.22 (br m, 1H), 3.15–3.05 (br m, 1H), 2.00 (s, 3H), 1.94–1.82 (br m, 1H), 1.79–1.57 (br m, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.07 (d, 3H, J = 6.7 Hz).

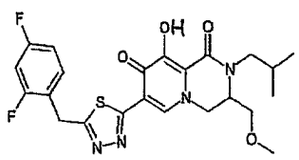
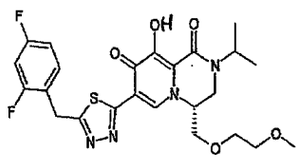
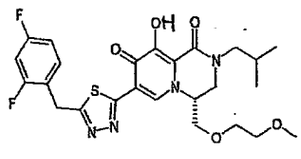
[0424]

[Table 1-8]

No.	structural formula	salt	^{1}H-NMR
40		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.92–12.53 (m, 1H), 8.44 (s, 1H), 7.97 (t, 1H, J = 6.3 Hz), 7.64 (s, 1H), 7.49–7.40 (m, 1H), 7.29–7.19 (m, 1H), 7.12–7.02 (m, 1H), 5.10–4.98 (m, 1H), 4.86–4.75 (m, 1H), 4.21 (s, 2H), 3.90–3.81 (m, 1H), 3.75–3.67 (m, 1H), 2.92–2.82 (m, 1H), 2.77–2.66 (m, 1H), 2.61–2.48 (m, 2H), 1.44–1.30 (m, 1H), 1.18 (d, 3H, J = 7.2 Hz), 1.15 (d, 3H, J = 7.2 Hz), 0.54 (d, 3H, J = 6.7 Hz), 0.50 (d, 3H, J = 7.2 Hz).
41		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.88–12.50 (m, 1H), 8.68 (s, 1H), 7.65 (s, 1H), 7.49–7.40 (m, 1H), 7.28–7.20 (m, 1H), 7.11–7.03 (m, 1H), 5.11–5.03 (m, 1H), 4.84–4.73 (m, 1H), 4.21 (s, 2H), 3.88–3.73 (m, 2H), 3.54–3.19 (m, 4H), 2.87 (d, 2H, J = 7.0 Hz), 1.59–1.43 (m, 2H), 1.42–1.29 (m, 4H), 1.13 (d, 3H, J = 6.7 Hz), 1.13 (d, 3H, J = 6.5 Hz).
42		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.45 (br s, 1H), 8.84 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.07 (m, 1H), 4.66 (dd, 1H, J = 13.4, 1.6 Hz), 4.49 (s, 2H), 4.47 (sep, 1H, J = 6.8 Hz), 4.35 (dd, 1H, J = 13.4, 3.7 Hz), 4.23–4.17 (m, 1H), 3.49 (dd, 1H, J = 10.2, 4.2 Hz), 3.39 (dd, 1H, J = 10.2, 7.4 Hz), 3.21 (s, 3H), 1.30 (d, 3H, J = 6.8 Hz), 1.28 (d, 3H, J = 6.8 Hz).

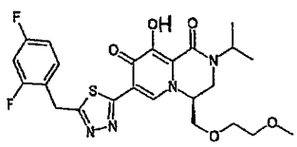
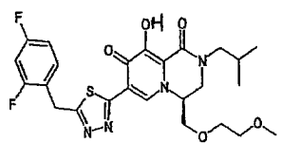
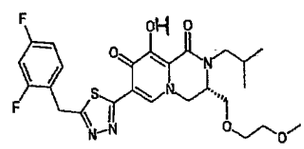
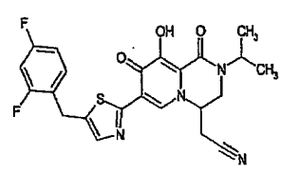
[0425]

[Table 1-9]

No.	structural formula	salt	^{1}H-NMR
43		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.54 (br s, 1H), 8.83 (s, 1H), 7.57-7.49 (m, 1H), 7.32-7.25 (m, 1H), 7.14-7.07 (m, 1H), 4.65 (dd, 1H, J = 13.4, 1.4 Hz), 4.48 (s, 2H), 4.47 (dd, 1H, J = 13.4, 4.3 Hz), 4.10-4.04 (m, 1H), 3.80 (dd, 1H, J = 13.3, 8.0 Hz), 3.53 (dd, 1H, J = 10.4, 5.1 Hz), 3.49 (dd, 1H, J = 10.4, 6.3 Hz), 3.20 (s, 3H), 2.94 (dd, 1H, J = 13.3, 7.1 Hz), 2.08 (ddsep, 1H, J = 8.0, 7.1, 6.7 Hz), 0.95 (d, 3H, J = 6.7 Hz), 0.89 (d, 3H, J = 6.7 Hz).
44		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.84 (br s, 1H), 8.81 (s, 1H), 7.59-7.49 (m, 1H), 7.33-7.23 (m, 1H), 7.16-7.07 (m, 1H), 4.99-4.90 (m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 3.93-3.60 (m, 4H), 3.58-3.44 (m, 2H), 3.33 (t, 2H, J = 4.6 Hz), 3.11 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
45		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.80 (br s, 1H), 8.80 (s, 1H), 7.59-7.50 (m, 1H), 7.35-7.24 (m, 1H), 7.16-7.07 (m, 1H), 4.97-4.86 (m, 1H), 4.49 (s, 2H), 4.06 (dd, 1H, J = 13.7, 4.2 Hz), 3.80-3.66 (m, 3H), 3.59-3.46 (m, 3H), 3.36-3.31 (m, 2H), 3.22 (dd, 1H, J = 7.1, 12.6 Hz), 3.11 (s, 3H), 2.00 (sept, 1H, J = 6.6 Hz), 0.91 (d, 6H, J = 6.6 Hz).

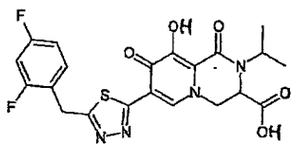
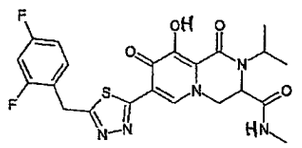
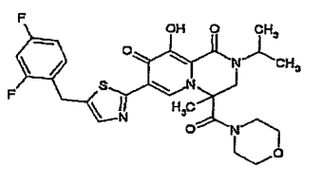
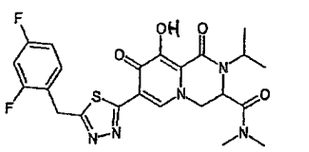
[0426]

[Table 1-10]

No.	structural formula	salt	^{1}H-NMR
46		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.84 (br s, 1H), 8.81 (s, 1H), 7.59–7.49 (m, 1H), 7.33–7.23 (m, 1H), 7.16–7.07 (m, 1H), 4.99–4.90 (m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 3.93–3.60 (m, 4H), 3.58–3.44 (m, 2H), 3.33 (t, 2H, J = 4.6 Hz), 3.11 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
47		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (br s, 1H), 8.80 (s, 1H), 7.59–7.50 (m, 1H), 7.35–7.24 (m, 1H), 7.16–7.07 (m, 1H), 4.97–4.86 (m, 1H), 4.49 (s, 2H), 4.06 (dd, 1H, J = 13.7, 4.2 Hz), 3.80–3.66 (m, 3H), 3.59–3.46 (m, 3H), 3.36–3.31 (m, 2H), 3.22 (dd, 1H, J = 7.1, 12.6 Hz), 3.11 (s, 3H), 2.00 (sept, 1H, J = 6.6 Hz), 0.91 (d, 6H, J = 6.6 Hz).
48		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.55 (br s, 1H), 8.81 (s, 1H), 7.59–7.49 (m, 1H), 7.35–7.24 (m, 1H), 7.16–7.07 (m, 1H), 4.65 (d, 1H, J = 13.2 Hz), 4.53–4.45 (m, 1H), 4.48 (s, 2H), 4.09–4.01 (m, 1H), 3.80 (dd, 1H, J = 13.4, 7.9 Hz), 3.67–3.57 (m, 2H), 3.50–3.39 (m, 2H), 3.30–3.24 (m, 2H), 3.08 (s, 3H), 2.95 (dd, 1H, J = 13.4, 7.0 Hz), 2.14–2.01 (m, 1H), 0.95 (d, 3H, J = 6.5 Hz), 0.90 (d, 3H, J = 6.7 Hz).
49		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.73 (br s, 1H), 8.80 (s, 1H), 7.67 (s, 1H), 7.51–7.42 (m, 1H), 7.29–7.20 (m, 1H), 7.12–7.03 (m, 1H), 5.27–5.17 (m, 1H), 4.85–4.72 (m, 1H), 4.22 (s, 2H), 3.96–3.65 (m, 2H), 3.34–3.20 (m, 2H), 1.20 (d, 3H, J = 7.2 Hz), 1.14 (d, 3H, J = 7.0 Hz).

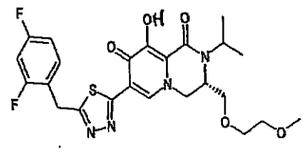
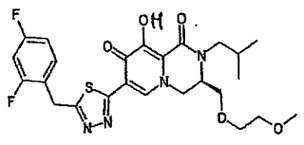
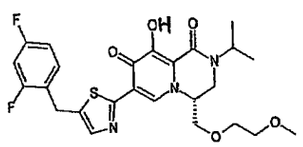
[0427]

[Table 1-11]

No.	structural formula	salt	^{1}H-NMR
50		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.38 (s, 1H), 8.95 (s, 1H), 7.57-7.50 (m, 1H), 7.32-7.25 (m, 1H), 7.14-7.08 (m, 1H), 5.00-4.91 (m, 2H), 4.73 (sep, 1H, J = 6.6 Hz), 4.52 (dd, 1H, J = 13.6, 3.9 Hz), 4.48 (s, 2H), 1.24 (d, 3H, J = 6.6 Hz), 1.13 (d, 3H, J = 6.6 Hz).
51		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.48 (s, 1H), 8.80 (s, 1H), 8.31 (q, 1H, J = 4.6 Hz), 7.57-7.49 (m, 1H), 7.33-7.24 (m, 1H), 7.14-7.07 (m, 1H), 4.76 (d, 1H, J = 14.2 Hz), 4.73 (sep, 1H, J = 6.8 Hz), 4.60 (d, 1H, J = 4.0 Hz), 4.54 (dd, 1H, J = 14.2, 4.0 Hz), 4.48 (s, 2H), 2.60 (d, 3H, J = 4.6 Hz), 1.21 (d, 3H, J = 6.8 Hz), 1.04 (d, 3H, J = 6.8 Hz).
52		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.95 (br s, 1H), 8.39 (s, 1H), 7.68 (s, 1H), 7.45 (td, 1H, J = 8.6, 6.7 Hz), 7.25 (ddd, 1H, J = 10.2, 9.3, 2.6 Hz), 7.07 (tdd, 1H, J = 8.6, 2.6, 0.9 Hz), 4.75 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.02 (d, 1H, J = 14.4 Hz), 3.81 (d, 1H, J = 14.4 Hz), 3.60-3.41 (br m, 8H), 1.91 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
53		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.57 (s, 1H), 8.81 (s, 1H), 7.57-7.49 (m, 1H), 7.32-7.25 (m, 1H), 7.14-7.07 (m, 1H), 5.17 (d, 1H, J = 3.0 Hz), 4.80 (d, 1H, J = 13.7 Hz), 4.70 (sep, 1H, J = 6.7 Hz), 4.52-4.46 (m, 1H), 4.48 (s, 2H), 3.20 (s, 3H), 2.81 (s, 3H), 1.24 (d, 3H, J = 6.7 Hz), 1.00 (d, 3H, J = 6.7 Hz).

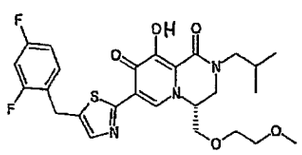
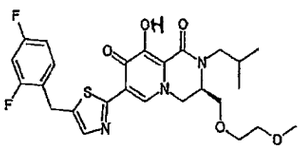
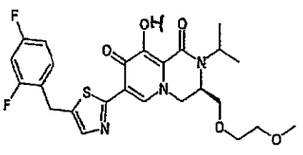
[0428]

[Table 1-12]

No.	structural formula	salt	^{1}H-NMR
54		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.44 (br s, 1H), 8.81 (s, 1H), 7.59–7.48 (m, 1H), 7.34–7.23 (m, 1H), 7.16–7.06 (m, 1H), 4.69–4.61 (m, 1H), 4.53–4.43 (m, 1H), 4.48 (s, 2H), 4.36 (dd, 1H, J = 7.2, 13.4 Hz), 4.23–4.14 (m, 1H), 3.51–3.40 (m, 4H), 3.33–3.25 (m, 2H), 3.08 (s, 3H), 1.28 (d, 3H, J = 6.7 Hz), 1.29 (d, 3H, J = 6.5 Hz).
55		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.55 (br s, 1H), 8.81 (s, 1H), 7.59–7.49 (m, 1H), 7.35–7.24 (m, 1H), 7.16–7.07 (m, 1H), 4.65 (d, 1H, J = 13.2 Hz), 4.53–4.45 (m, 1H), 4.48 (s, 2H), 4.09–4.01 (m, 1H), 3.80 (dd, 1H, J = 13.4, 7.9 Hz), 3.67–3.57 (m, 2H), 3.50–3.39 (m, 2H), 3.30–3.24 (m, 2H), 3.08 (s, 3H), 2.95 (dd, 1H, J = 13.4, 7.0 Hz), 2.14–2.01 (m, 1H), 0.95 (d, 3H, J = 6.5 Hz), 0.90 (d, 3H, J = 6.7 Hz).
56		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.70 (br s, 1H), 8.65 (s, 1H), 7.65 (s, 1H), 7.49–7.42 (m, 1H), 7.28–7.21 (m, 1H), 7.10–7.04 (m, 1H), 4.93–4.87 (m, 1H), 4.77 (sep, 1H, J = 6.9 Hz), 4.21 (s, 2H), 3.82 (dd, 1H, J = 13.7, 4.0 Hz), 3.76–3.67 (m, 2H), 3.62 (dd, 1H, J = 10.5, 7.7 Hz), 3.56–3.45 (m, 2H), 3.35–3.32 (m, 2H), 3.12 (s, 3H), 1.16 (d, 3H, J = 6.9 Hz), 1.15 (d, 3H, J = 6.9 Hz).

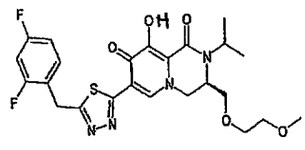
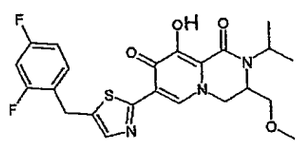
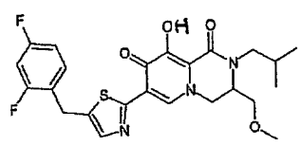
[0429]

[Table 1-13]

No.	structural formula	salt	^{1}H-NMR
57		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.66 (br s, 1H), 8.64 (s, 1H), 7.65 (s, 1H), 7.49–7.42 (m, 1H), 7.28–7.21 (m, 1H), 7.10–7.04 (m, 1H), 4.90–4.82 (m, 1H), 4.21 (s, 2H), 4.04 (dd, 1H, J = 13.7, 4.4 Hz), 3.78–3.64 (m, 3H), 3.56–3.45 (m, 2H), 3.45–3.28 (m, 3H), 3.21 (dd, 1H, J = 13.3, 6.9 Hz), 3.11 (s, 3H), 2.05–1.94 (m, 1H), 0.91 (d, 6H, J = 6.4 Hz).
58		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.40 (br s, 1H), 8.63 (s, 1H), 7.64 (s, 1H), 7.49–7.41 (m, 1H), 7.28–7.20 (m, 1H), 7.11–7.04 (m, 1H), 4.62–4.55 (m, 1H), 4.46 (dd, 1H, J = 13.8, 4.4 Hz), 4.21 (s, 2H), 4.06–4.00 (m, 1H), 3.80 (dd, 1H, J = 13.4, 7.7 Hz), 3.64–3.54 (m, 2H), 3.50–3.40 (m, 2H), 3.33–3.24 (m, 2H), 3.10 (s, 3H), 2.94 (dd, 1H, J = 13.4, 7.1 Hz), 2.12–2.03 (m, 1H), 0.95 (d, 3H, J = 6.7 Hz), 0.89 (d, 3H, J = 6.7 Hz).
59		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.30 (br s, 1H), 8.62 (s, 1H), 7.64 (s, 1H), 7.50–7.40 (m, 1H), 7.29–7.20 (m, 1H), 7.12–7.03 (m, 1H), 4.62–4.55 (m, 1H), 4.48 (sep, 1H, J = 6.7 Hz), 4.36–4.31 (m, 1H), 4.21 (s, 2H), 4.19–4.14 (m, 1H), 3.58 (dd, 1H, J = 10.3, 4.1 Hz), 3.52–3.39 (m, 3H), 3.33–3.27 (m, 2H), 3.10 (s, 3H), 1.29 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).

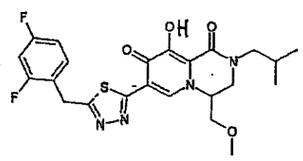
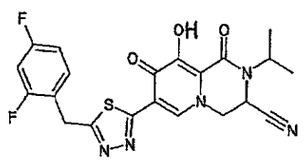
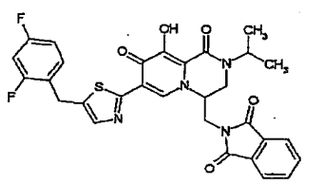
[0430]

[Table 1-14]

No.	structural formula	salt	^{1}H-NMR
60		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.44 (br s, 1H), 8.81 (s, 1H), 7.59–7.48 (m, 1H), 7.34–7.23 (m, 1H), 7.16–7.06 (m, 1H), 4.69–4.61 (m, 1H), 4.53–4.43 (m, 1H), 4.48 (s, 2H), 4.36 (dd, 1H, J = 7.2, 13.4 Hz), 4.23–4.14 (m, 1H), 3.51–3.40 (m, 4H), 3.33–3.25 (m, 2H), 3.08 (s, 3H), 1.28 (d, 3H, J = 6.7 Hz), 1.29 (d, 3H, J = 6.5 Hz).
61		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.66 (s, 1H), 7.49–7.41 (m, 1H), 7.29–7.21 (m, 1H), 7.11–7.03 (m, 1H), 4.60 (dd, 1H, J = 13.4, 1.4 Hz), 4.47 (sep, 1H, J = 6.8Hz), 4.33 (dd, 1H, J = 13.4, 3.7 Hz), 4.22 (s, 2H), 4.14–4.10 (m, 1H), 3.48 (dd, 1H, J = 10.3, 4.3 Hz), 3.36 (dd, 1H, J = 10.3, 7.7 Hz), 3.21 (s, 3H), 1.29 (d, 3H, J = 6.8 Hz), 1.28 (d, 3H, J = 6.8 Hz).
62		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.42 (br s, 1H), 8.65 (s, 1H), 7.65 (s, 1H), 7.50–7.41 (m, 1H), 7.30–7.21 (m, 1H), 7.11–7.03 (m, 1H), 4.59 (dd, 1H, J = 13.7, 1.2 Hz), 4.46 (dd, 1H, J = 13.7, 4.2 Hz), 4.21 (s, 2H), 4.08–4.01 (m, 1H), 3.80 (dd, 1H, J = 13.2, 7.9 Hz), 3.52 (dd, 1H, J = 10.4, 5.4 Hz), 3.48 (dd, 1H, J = 10.4, 6.4 Hz), 3.20 (s, 3H), 2.93 (dd, 1H, J = 13.2, 7.2 Hz), 2.08 (tt, 1H, J = 6.7, 6.7 Hz), 0.95 (d, 3H, J = 6.7 Hz), 0.89 (d, 3H, J = 6.7 Hz).

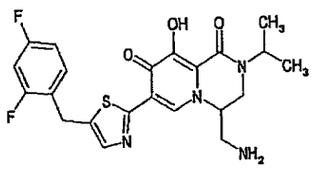
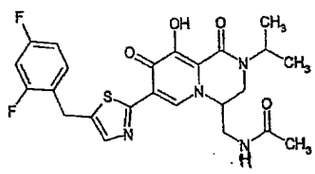
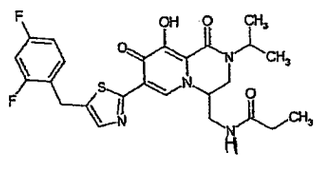
[0431]

[Table 1-15]

No.	structural formula	salt	^{1}H-NMR
63		HCl	^{1}H-NMR ($CDCl_3$) δ : 12.78 (br s, 1H), 9.36 (s, 1H), 7.38–7.30 (m, 1H), 6.92–6.84 (m, 2H), 4.58–4.51 (m, 1H), 4.48 (s, 2H), 4.05–3.98 (m, 1H), 3.76–3.63 (m, 3H), 3.51 (dd, 1H, J = 13.4, 7.9 Hz), 3.39 (s, 3H), 3.29 (dd, 1H, J = 13.4, 7.0 Hz), 2.09–1.99 (m, 1H), 1.00 (d, 3H, J = 6.7 Hz), 0.99 (d, 3H, J = 6.7 Hz).
64		HCl	^{1}H-NMR (DMSO-d_6) δ : 9.03 (s, 1H), 7.59–7.51 (m, 1H), 7.33–7.25 (m, 1H), 7.16–7.08 (m, 1H), 5.66 (dd, 1H, J = 3.0, 1.9 Hz), 5.07 (dd, 1H, J = 13.8, 1.9 Hz), 4.78 (sep, 1H, J = 6.8 Hz), 4.61 (dd, 1H, J = 13.8, 3.0 Hz), 4.51 (s, 2H), 1.31 (d, 3H, J = 6.8 Hz), 1.24 (d, 3H, J = 6.8 Hz).
65		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.31 (s, 1H), 7.78–7.73 (m, 2H), 7.72–7.67 (m, 2H), 7.38 (td, 1H, J = 8.8, 6.8 Hz), 7.36 (s, 1H), 7.25 (ddd, 1H, J = 10.4, 9.0, 2.6 Hz), 7.08 (tdd, 1H, J = 8.8, 2.6, 0.9 Hz), 4.99–4.91 (br m, 1H), 4.80 (sep, 1H, J = 6.7 Hz), 4.13 (s, 2H), 4.04 (dd, 1H, J = 14.3, 4.6 Hz), 3.96 (dd, 1H, J = 13.9, 2.0 Hz), 3.89 (dd, 1H, J = 13.9, 4.0 Hz), 3.82 (dd, 1H, J = 14.3, 9.3 Hz), 1.27 (d, 3H, J = 6.7 Hz), 1.19 (d, 3H, J = 6.7 Hz).

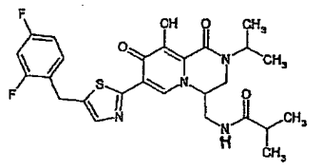
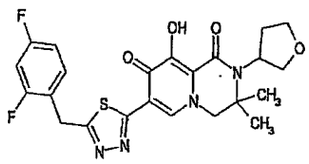
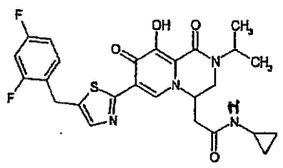
[0432]

[Table 1-16]

No.	structural formula	salt	^{1}H-NMR
66		2HCl	^{1}H-NMR (DMSO-d_6) δ: 12.56 (br s, 1H), 8.70 (s, 1H), 8.25-8.13 (br m, 2H), 7.66 (s, 1H), 7.45 (td, 1H, J = 8.7, 6.7 Hz), 7.25 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.08 (tdd, 1H, J = 8.7, 2.6, 0.9 Hz), 4.95-4.86 (br m, 1H), 4.76 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 3.90 (dd, 1H, J = 13.8, 3.6 Hz), 3.84 (dd, 1H, J = 13.8, 1.9 Hz), 3.35-3.24 (br m, 1H), 3.22-3.09 (br m, 1H), 1.19 (d, 3H, J = 6.7 Hz), 1.15 (d, 3H, J = 6.7 Hz).
67		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.68 (br s, 1H), 8.39 (s, 1H), 8.05 (t, 1H, J = 6.0 Hz), 7.64 (s, 1H), 7.46 (td, 1H, J = 8.8, 7.0 Hz), 7.25 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.08 (tdd, 1H, J = 8.8, 2.6, 0.9 Hz), 4.77 (sep, 1H, J = 6.7 Hz), 4.67-4.59 (br m, 1H), 4.21 (s, 2H), 3.84 (dd, 1H, J = 13.8, 3.8 Hz), 3.74 (dd, 1H, J = 13.8, 0.9 Hz), 3.41-3.27 (m, 2H), 1.66 (s, 3H), 1.19 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
68		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.68 (br s, 1H), 8.36 (s, 1H), 7.97 (t, 1H, J = 6.0 Hz), 7.62 (s, 1H), 7.45 (td, 1H, J = 8.7, 6.7 Hz), 7.25 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.08 (tdd, 1H, J = 8.7, 2.6, 0.9 Hz), 4.77 (sep, 1H, J = 6.7 Hz), 4.68-4.60 (br m, 1H), 4.21 (s, 2H), 3.84 (dd, 1H, J = 13.7, 3.9 Hz), 3.75 (dd, 1H, J = 13.7, 1.4 Hz), 3.40-3.29 (m, 2H), 1.96-1.86 (m, 2H), 1.19 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz), 0.78 (t, 3H, J = 7.5 Hz).

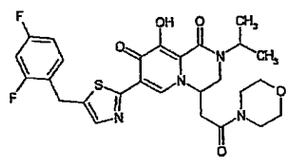
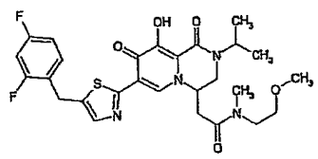
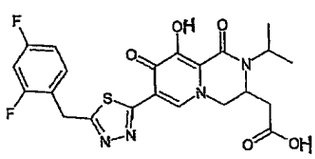
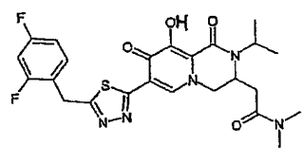
[0433]

[Table 1-17]

No.	structural formula	salt	^{1}H-NMR
69		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.66 (s, 1H), 8.33 (s, 1H), 7.93 (t, 1H, J = 6.0 Hz), 7.61 (s, 1H), 7.43 (td, 1H, J = 8.7, 6.6 Hz), 7.25 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.07 (tdd, 1H, J = 8.7, 2.6, 0.9 Hz), 4.78 (sep, 1H, J = 6.7 Hz), 4.69–4.61 (br m, 1H), 4.20 (s, 2H), 3.84 (dd, 1H, J = 13.7, 3.9 Hz), 3.74 (dd, 1H, J = 13.7, 1.4 Hz), 3.38–3.32 (m, 2H), 2.15 (sep, 1H, J = 6.7 Hz), 1.19 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz), 0.85 (d, 3H, J = 6.7 Hz), 0.73 (d, 3H, J = 6.7 Hz).
70		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.55 (br s, 1H), 8.75 (s, 1H), 7.58–7.50 (m, 1H), 7.34–7.24 (m, 1H), 7.16–7.07 (m, 1H), 4.49 (s, 2H), 4.43–4.30 (m, 3H), 4.03 (q, 1H, J = 7.8 Hz), 3.92–3.48 (m, 3H), 2.36–2.26 (m, 1H), 2.12–2.00 (m, 1H), 1.39 (s, 3H), 1.36 (s, 3H).
71		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.64 (br s, 1H), 8.49 (s, 1H), 8.04 (d, 1H, J = 3.9 Hz), 7.65 (s, 1H), 7.50–7.40 (m, 1H), 7.29–7.20 (m, 1H), 7.11–7.03 (m, 1H), 5.07–4.96 (m, 1H), 4.84–4.72 (m, 1H), 4.21 (s, 2H), 3.87–3.59 (m, 2H), 2.71–2.30 (m, 3H), 1.15 (t, 6H, J = 7.4 Hz), 0.55–0.35 (m, 2H), 0.24–0.06 (m, 2H).

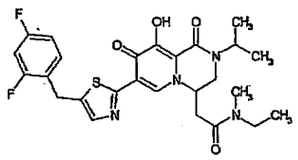
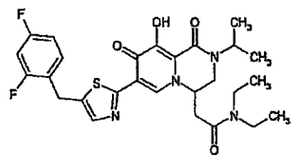
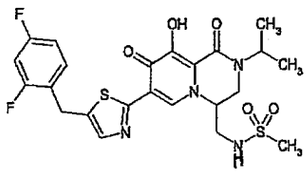
[0434]

[Table 1-18]

No.	structural formula	salt	^{1}H-NMR
72		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.69 (br s, 1H), 8.70 (s, 1H), 7.65 (s, 1H), 7.49–7.39 (m, 1H), 7.29–7.19 (m, 1H), 7.11–7.00 (m, 1H), 5.14–5.01 (m, 1H), 4.86–4.71 (m, 1H), 4.21 (s, 2H), 3.91–3.67 (m, 2H), 3.51–3.22 (m, 8H), 2.91 (d, 2H, J = 6.5 Hz), 1.14 (d, 3H, J = 6.7 Hz), 1.13 (d, 3H, J = 6.7 Hz).
73		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.69 (s, 1.0H), 7.65 (s, 1.0H), 7.49–7.40 (m, 1.0H), 7.29–7.19 (m, 1.0H), 7.11–7.02 (m, 1.0H), 5.13–5.03 (m, 1.0H), 4.84–4.72 (m, 1.0H), 4.21 (s, 2.0H), 3.88–3.55 (m, 2.0H), 3.55–3.25 (m, 4.0H), 3.15 (s, 1.5H), 3.12 (s, 1.5H), 3.02–2.82 (m, 2.0H), 2.88 (s, 1.5H), 2.79 (s, 1.5H), 1.13 (d, 6.0H, J = 6.5 Hz).
74		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.85 (s, 1H), 7.57–7.50 (m, 1H), 7.32–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.62–4.56 (m, 1H), 4.53–4.30 (m, 3H), 4.49 (s, 2H), 2.69–2.45 (m, 2H), 1.30 (d, 3H, J = 7.2 Hz), 1.28 (d, 3H, J = 7.2 Hz).
75		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.50 (s, 1H), 8.80 (s, 1H), 7.57–7.49 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.57–4.46 (m, 2H), 4.48 (s, 2H), 4.45–4.34 (m, 2H), 2.84 (s, 3H), 2.83 (s, 3H), 2.81–2.54 (m, 2H), 1.28 (d, 3H, J = 6.8 Hz), 1.25 (d, 3H, J = 6.8 Hz).

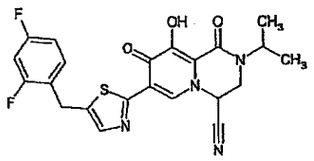
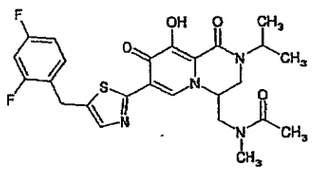
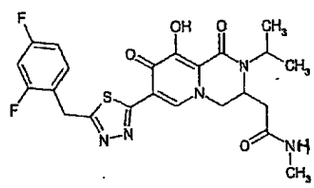
[0435]

[Table 1-19]

No.	structural formula	salt	^{1}H-NMR
76		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.81-12.55 (m, 1H), 8.70 (d, 1H, J = 3.7 Hz), 7.65 (s, 1H), 7.50-7.40 (m, 1H), 7.29-7.19 (m, 1H), 7.11-7.03 (m, 1H), 5.13-5.02 (m, 1H), 4.86-4.72 (m, 1H), 4.21 (s, 2H), 3.88-3.73 (m, 2H), 3.42-3.10 (m, 3H), 2.90-2.80 (m, 1H), 2.83 (s, 1.8H), 2.76 (s, 1.2H), 1.13 (d, 3H, J = 7.0 Hz), 1.12 (d, 3H, J = 6.7 Hz), 0.99 (t, 1.2H, J = 7.2 Hz), 0.93 (t, 1.8H, J = 7.4 Hz).
77		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.67 (br s, 1H), 8.68 (s, 1H), 7.65 (s, 1H), 7.50-7.40 (m, 1H), 7.29-7.19 (m, 1H), 7.12-7.03 (m, 1H), 5.14-5.04 (m, 1H), 4.85-4.73 (m, 1H), 4.21 (s, 2H), 3.90-3.76 (m, 2H), 3.35-3.10 (m, 4H), 2.84 (d, 2H, J = 6.7 Hz), 1.13 (t, 6H, J = 6.7 Hz), 0.98 (t, 3H, J = 7.4 Hz), 0.94 (t, 3H, J = 7.4 Hz).
78		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.66 (br s, 1H), 8.57 (s, 1H), 7.65 (s, 1H), 7.45 (td, 1H, J = 8.7, 6.6 Hz), 7.36 (dd, 1H, J = 6.7, 6.1 Hz), 7.24 (ddd, 1H, J = 10.4, 9.5, 2.8 Hz), 7.07 (tdd, 1H, J = 8.7, 2.8, 0.9 Hz), 4.75 (sep, 1H, J = 6.7 Hz), 4.71-4.63 (br m, 1H), 4.21 (s, 2H), 3.85 (dd, 1H, J = 13.8, 4.1 Hz), 3.75 (dd, 1H, J = 13.8, 1.2 Hz), 3.38 (ddd, 1H, J = 14.1, 6.1, 5.6 Hz), 3.16 (ddd, 1H, J = 14.1, 9.0, 6.7 Hz), 2.89 (s, 3H), 1.21 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).

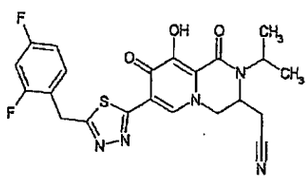
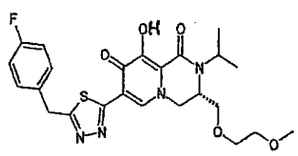
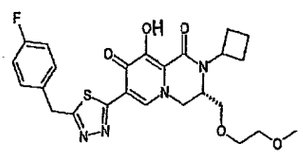
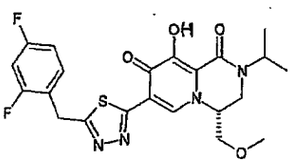
[0436]

[Table 1-20]

No.	structural formula	salt	^{1}H-NMR
79		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.94 (s, 1H), 7.70 (s, 1H), 7.47 (td, 1H, J = 8.6, 6.8 Hz), 7.25 (ddd, 1H, J = 10.1, 9.5, 2.6 Hz), 7.08 (tdd, 1H, J = 8.6, 2.6, 1.1 Hz), 6.30-6.25 (br m, 1H), 4.80 (sep, 1H, J = 6.8 Hz), 4.24 (dd, 1H, J = 14.1, 2.0 Hz), 4.23 (s, 2H), 4.02 (dd, 1H, J = 14.1, 3.5 Hz), 1.23 (d, 3H, J = 6.8 Hz), 1.16 (d, 3H, J = 6.8 Hz).
80		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.35 (s, 1H), 7.64 (s, 1H), 7.46 (td, 1H, J = 8.8, 7.1 Hz), 7.25 (ddd, 1H, J = 10.6, 9.5, 2.6 Hz), 7.08 (tdd, 1H, J = 8.8, 2.6, 1.3 Hz), 4.92-4.84 (br m, 1H), 4.78 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 3.87 (dd, 1H, J = 14.1, 4.4 Hz), 3.83 (dd, 1H, J = 14.1, 10.8 Hz), 3.71 (dd, 1H, J = 13.9, 1.1 Hz), 3.39 (dd, 1H, J = 13.9, 4.0 Hz), 2.90 (s, 3H), 1.77 (s, 3H), 1.19 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
81		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.42 (s, 1H), 8.80 (s, 1H), 7.92 (q, 1H, J = 4.4 Hz), 7.57-7.50 (m, 1H), 7.33-7.26 (m, 1H), 7.15-7.08 (m, 1H), 4.53-4.30 (m, 4H), 4.49 (s, 2H), 2.56 (d, 3H, J = 4.4 Hz), 2.44-2.37 (m, 2H), 1.29 (d, 3H, J = 6.8 Hz), 1.27 (d, 3H, J = 6.8 Hz).

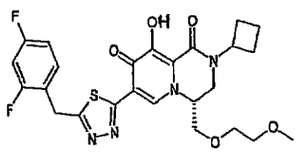
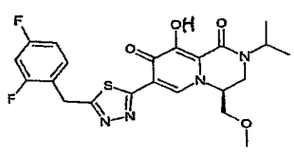
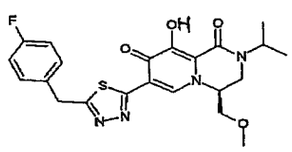
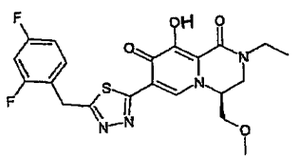
[0437]

[Table 1-21]

No.	structural formula	salt	^{1}H-NMR
82		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.88 (s, 1H), 7.58–7.50 (m, 1H), 7.32–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.64 (d, 1H, J = 13.2 Hz), 4.54–4.41 (m, 3H), 4.49 (s, 2H), 3.12 (dd, 1H, J = 17.5, 7.0 Hz), 3.01 (dd, 1H, J = 17.5, 4.2 Hz), 1.31 (d, 3H, J = 6.8 Hz), 1.31 (d, 3H, J = 6.8 Hz).
83		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.42 (br s, 1H), 8.82 (s, 1H), 7.44–7.37 (m, 2H), 7.22–7.14 (m, 2H), 4.68–4.62 (m, 1H), 4.55–4.42 (m, 1H), 4.47 (s, 2H), 4.36 (dd, 1H, J = 13.1, 3.6 Hz), 4.23–4.13 (m, 1H), 3.52–3.39 (m, 4H), 3.32–3.25 (m, 2H), 3.09 (s, 3H), 1.29 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).
84		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.48 (br s, 1H), 8.82 (s, 1H), 7.44–7.36 (m, 2H), 7.22–7.15 (m, 2H), 4.70–4.64 (m, 1H), 4.61–4.50 (m, 1H), 4.47 (s, 2H), 4.45–4.37 (m, 1H), 4.31–4.23 (m, 1H), 3.58–3.39 (m, 4H), 3.31–3.25 (m, 2H), 3.09 (s, 3H), 2.37–2.12 (m, 4H), 1.75–1.62 (m, 2H).
85		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.82 (s, 1H), 8.80 (s, 1H), 7.54 (td, 1H, J = 8.8, 6.7 Hz), 7.29 (ddd, 1H, J = 10.2, 9.3, 2.6 Hz), 7.12 (tdd, 1H, J = 8.8, 2.6 0.9 Hz), 5.01–4.93 (br m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 3.84 (dd, 1H, J = 13.9, 3.9 Hz), 3.75 (dd, 1H, J = 13.9, 1.4 Hz), 3.62 (dd, 1H, J = 10.2, 5.8 Hz), 3.57 (dd, 1H, J = 10.2, 7.7 Hz), 3.25 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).

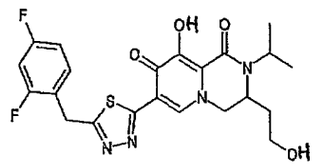
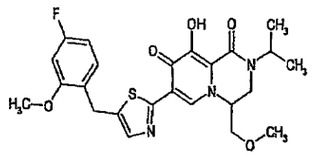
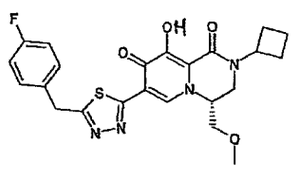
[0438]

[Table 1-22]

No.	structural formula	salt	^{1}H-NMR
86		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.73 (br s, 1H), 8.82 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 5.00–4.84 (m, 2H), 4.49 (s, 2H), 3.98–3.87 (m, 2H), 3.74 (dd, 1H, J = 10.4, 6.0 Hz), 3.64 (dd, 1H, J = 10.4, 7.4 Hz), 3.58–3.46 (m, 2H), 3.34 (t, 2H, J = 4.6 Hz), 3.12 (s, 3H), 2.34–2.03 (m, 4H), 1.76–1.65 (m, 2H).
87		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.80 (s, 1H), 7.59–7.49 (m, 1H), 7.35–7.24 (m, 1H), 7.16–7.07 (m, 1H), 5.01–4.93 (m, 1H), 4.77 (t, 1H, J = 6.7 Hz), 4.49 (s, 2H), 3.84 (dd, 1H, J = 13.7, 3.9 Hz), 3.75 (dd, 1H, J = 13.7, 2.5 Hz), 3.62 (dd, 1H, J = 10.2, 5.8 Hz), 3.57 (dd, 1H, J = 10.2, 7.7 Hz), 3.25 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
88		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.82 (br s, 1H), 8.80 (s, 1H), 7.45–7.39 (m, 2H), 7.22–7.15 (m, 2H), 5.01–4.94 (m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 3.84 (dd, 1H, J = 13.7, 3.9 Hz), 3.75 (dd, 1H, J = 13.7, 1.6 Hz), 3.62 (dd, 1H, J = 10.4, 5.8 Hz), 3.57 (dd, 1H, J = 10.4, 7.7 Hz), 3.25 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
89		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.76 (br s, 1H), 8.78 (s, 1H), 7.58–7.50 (m, 1H), 7.32–7.26 (m, 1H), 7.14–7.08 (m, 1H), 4.99–4.89 (m, 1H), 4.49 (s, 2H), 4.07 (dd, 1H, J = 13.7, 4.4 Hz), 3.74–3.56 (m, 4H), 3.44–3.33 (m, 1H), 3.25 (s, 3H), 1.14 (t, 3H, J = 7.2 Hz).

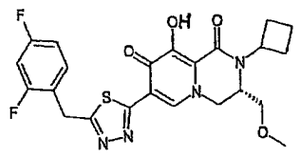
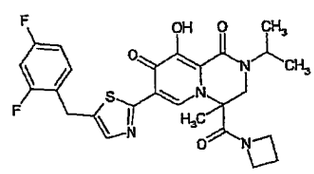
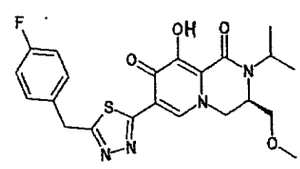
[0439]

[Table 1-23]

No.	structural formula	salt	^{1}H-NMR
90		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.47 (s, 1H), 8.87 (s, 1H), 7.57–7.49 (m, 1H), 7.32–7.24 (m, 1H), 7.15–7.07 (m, 1H), 4.66 (dd, 1H, J = 13.5, 1.7 Hz), 4.53 (sep, 1H, J = 6.8 Hz), 4.49 (s, 2H), 4.35–4.28 (m, 1H), 4.14–4.07 (m, 1H), 3.62–3.47 (m, 2H), 1.81–1.51 (m, 2H), 1.29 (d, 6H, J = 6.8 Hz).
91		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.76–12.55 (br m, 1H), 8.61 (s, 1H), 7.61 (s, 1H), 7.25 (dd, 1H, J = 8.5, 6.9 Hz), 6.92 (dd, 1H, J = 11.3, 2.4 Hz), 6.73 (td, 1H, J = 8.5, 2.4 Hz), 4.94–4.86 (br m, 1H), 4.77 (sep, 1H, J = 6.9 Hz), 4.09 (s, 2H), 3.84–3.79 (m, 1H), 3.83 (s, 3H), 3.76–3.69 (m, 1H), 3.60 (dd, 1H, J = 10.5, 5.6 Hz), 3.54 (dd, 1H, J = 10.5, 7.7 Hz), 3.23 (s, 3H), 1.16 (d, 3H, J = 6.9 Hz), 1.15 (d, 3H, J = 6.9 Hz).
92		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.70 (br s, 1H), 8.81 (s, 1H), 7.45–7.38 (m, 2H), 7.22–7.15 (m, 2H), 5.02–4.85 (m, 2H), 4.47 (s, 2H), 3.98–3.87 (m, 2H), 3.65 (dd, 1H, J = 10.3, 5.8 Hz), 3.57 (dd, 1H, J = 10.3, 7.5 Hz), 3.25 (s, 3H), 2.31–2.04 (m, 4H), 1.77–1.65 (m, 2H).

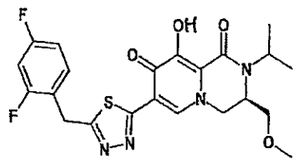
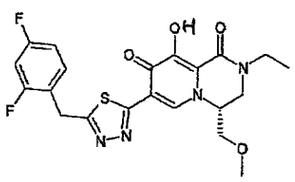
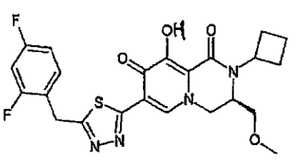
[0440]

[Table 1-24]

No.	structural formula	salt	^{1}H-NMR
93		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.84 (s, 1H), 7.57–7.49 (m, 1H), 7.32–7.25 (m, 1H), 7.15–7.07 (m, 1H), 4.68 (d, 1H, J = 13.2 Hz), 4.60–4.49 (m, 1H), 4.48 (s, 2H), 4.41 (dd, 1H, J = 13.2, 3.7 Hz), 4.32–4.25 (m, 1H), 3.43 (dd, 1H, J = 10.4, 4.6 Hz), 3.39 (dd, 1H, J = 10.4, 6.8 Hz), 3.21 (s, 3H), 2.39–2.11 (m, 4H), 1.77–1.63 (m, 2H).
94		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.79 (br s, 1H), 8.60 (s, 1H), 7.67 (s, 1H), 7.45 (td, 1H, J = 8.2, 6.0 Hz), 7.24 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.07 (tdd, 1H, J = 8.2, 2.6, 0.9 Hz), 4.70 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.19–4.14 (br m, 1H), 4.09 (d, 1H, J = 14.1 Hz), 4.00 (d, 1H, J = 14.1 Hz), 3.88–3.81 (br m, 2H), 3.74–3.69 (br m, 1H), 2.14–2.04 (br m, 2H), 1.94 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.13 (d, 3H, J = 6.7 Hz).
95		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.84 (s, 1H), 7.43–7.38 (m, 2H), 7.21–7.14 (m, 2H), 4.66 (d, 1H, J = 13.2 Hz), 4.47 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 4.34 (dd, 1H, J = 13.5, 3.7 Hz), 4.22–4.17 (m, 1H), 3.49 (dd, 1H, J = 10.6, 4.3 Hz), 3.39 (dd, 1H, J = 10.6, 7.5 Hz), 3.21 (s, 3H), 1.30 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).

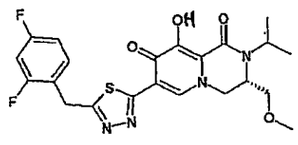
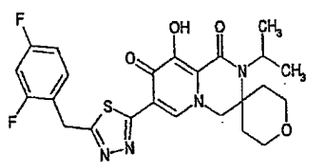
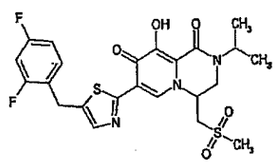
[0441]

[Table 1-25]

No.	structural formula	salt	^{1}H-NMR
96		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.45 (br s, 1H), 8.84 (s, 1H), 7.58-7.50 (m, 1H), 7.33-7.25 (m, 1H), 7.15-7.07 (m, 1H), 4.66 (dd, 1H, J = 13.4, 1.6 Hz), 4.49 (s, 2H), 4.47 (sep, 1H, J = 6.8 Hz), 4.35 (dd, 1H, J = 13.4, 3.7 Hz), 4.23-4.17 (m, 1H), 3.49 (dd, 1H, J = 10.2, 4.2 Hz), 3.39 (dd, 1H, J = 10.2, 7.4 Hz), 3.21 (s, 3H), 1.30 (d, 3H, J = 6.8 Hz), 1.28 (d, 3H, J = 6.8 Hz).
97		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.76 (br s, 1H), 8.78 (s, 1H), 7.58-7.50 (m, 1H), 7.32-7.26 (m, 1H), 7.14-7.08 (m, 1H), 4.99-4.89 (m, 1H), 4.49 (s, 2H), 4.07 (dd, 1H, J = 13.7, 4.4 Hz), 3.74-3.56 (m, 4H), 3.44-3.33 (m, 1H), 3.25 (s, 3H), 1.14 (t, 3H, J = 7.2 Hz).
98		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.51 (br s, 1H), 8.84 (s, 1H), 7.58-7.49 (m, 1H), 7.33-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.71-4.64 (m, 1H), 4.60-4.46 (m, 3H), 4.41 (dd, 1H, J = 13.7, 3.9 Hz), 4.31-4.25 (m, 1H), 3.46-3.36 (m, 2H), 3.21 (s, 3H), 2.37-2.12 (m, 4H), 1.77-1.64 (m, 2H).

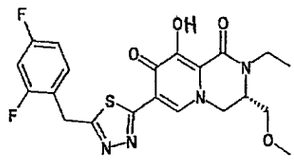
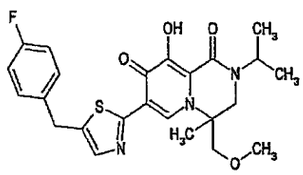
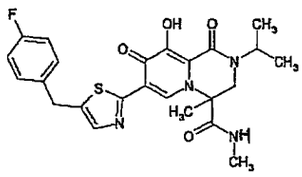
[0442]

[Table 1-26]

No.	structural formula	salt	^{1}H-NMR
99		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.46 (br s, 1H), 8.84 (s, 1H), 7.57–7.50 (m, 1H), 7.32–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.66 (dd, 1H, J = 13.2, 1.6 Hz), 4.52–4.42 (m, 1H), 4.49 (s, 2H), 4.35 (dd, 1H, J = 13.2, 4.0 Hz), 4.23–4.17 (m, 1H), 3.49 (dd, 1H, J = 10.4, 4.3 Hz), 3.39 (dd, 1H, J = 10.4, 7.5 Hz), 3.21 (s, 3H), 1.30 (d, 3H, J = 6.8 Hz), 1.28 (d, 3H, J = 6.8 Hz).
100		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.56 (br s, 1H), 9.02 (s, 1H), 7.53 (td, 1H, J = 8.5, 6.4 Hz), 7.29 (ddd, 1H, J = 10.5, 9.7, 2.4 Hz), 7.12 (tdd, 1H, J = 8.5, 2.4, 1.2 Hz), 4.72 (s, 2H), 4.49 (s, 2H), 4.16–4.02 (br m, 1H), 3.82–3.78 (m, 2H), 3.74–3.66 (m, 2H), 2.21–2.13 (m, 2H), 1.64–1.58 (m, 2H), 1.43 (d, 6H, J = 6.4 Hz).
101		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.66 (br s, 1H), 8.66 (s, 1H), 7.66 (s, 1H), 7.51–7.40 (m, 1H), 7.29–7.20 (m, 1H), 7.11–7.03 (m, 1H), 5.45–5.34 (m, 1H), 4.83–4.70 (m, 1H), 4.21 (s, 2H), 3.95–3.85 (m, 2H), 3.81–3.59 (m, 2H), 3.05 (s, 3H), 1.20 (d, 3H, J = 6.7 Hz), 1.14 (d, 3H, J = 6.7 Hz).

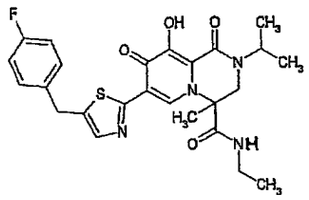
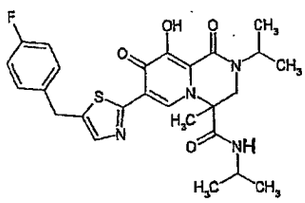
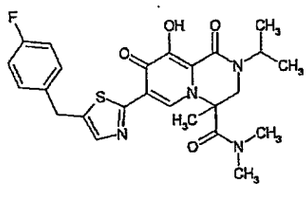
[0443]

[Table 1-27]

No.	structural formula	salt	^{1}H-NMR
102		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.50 (br s, 1H), 8.83 (s, 1H), 7.57-7.50 (m, 1H), 7.33-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.64 (dd, 1H, J = 13.7, 1.6 Hz), 4.49 (s, 2H), 4.43 (dd, 1H, J = 13.7, 4.1 Hz), 4.17-4.12 (m, 1H), 3.86 (dq, 1H, J = 13.4, 7.0 Hz), 3.54 (dd, 1H, J = 10.2, 5.1 Hz), 3.50 (dd, 1H, J = 10.2, 6.3 Hz), 3.27 (dq, 1H, J = 13.4, 7.0 Hz), 3.21 (s, 3H), 1.18 (t, 3H, J = 7.0 Hz).
103		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.61 (s, 1H), 7.70 (s, 1H), 7.36-7.29 (m, 2H), 7.18-7.11 (m, 2H), 4.80 (sep, 1H, J = 6.7 Hz), 4.20 (s, 2H), 3.74 (d, 1H, J = 13.7 Hz), 3.64 (d, 1H, J = 10.4 Hz), 3.64 (d, 1H, J = 13.7 Hz), 3.58 (d, 1H, J = 10.4 Hz), 3.24 (s, 3H), 1.63 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz).
104		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.79 (br s, 1H), 8.53 (s, 1H), 8.14 (q, 1H, J = 4.4 Hz), 7.69 (s, 1H), 7.36-7.30 (m, 2H), 7.18-7.11 (m, 2H), 4.70 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.09 (d, 1H, J = 13.9 Hz), 3.77 (d, 1H, J = 13.9 Hz), 2.60 (d, 3H, J = 4.4 Hz), 1.93 (s, 3H), 1.14 (d, 3H, J = 6.7 Hz), 1.09 (d, 3H, J = 6.7 Hz).

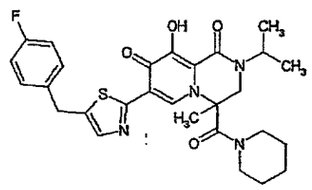
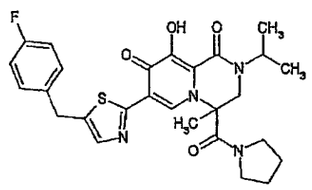
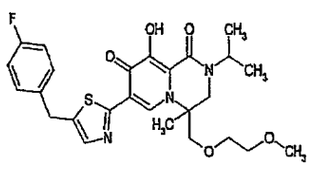
[0444]

[Table 1-28]

No.	structural formula	salt	^{1}H-NMR
105		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (br s, 1H), 8.52 (s, 1H), 8.18 (t, 1H, J = 5.2 Hz), 7.68 (s, 1H), 7.36–7.30 (m, 2H), 7.18–7.11 (m, 2H), 4.71 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.11 (d, 1H, J = 13.9 Hz), 3.78 (d, 1H, J = 13.9 Hz), 3.18–2.98 (m, 2H), 1.92 (s, 3H), 1.15 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz), 1.00 (t, 3H, J = 7.2 Hz).
106		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.84 (br s, 1H), 8.50 (s, 1H), 8.07 (d, 1H, J = 7.4 Hz), 7.68 (s, 1H), 7.36–7.30 (m, 2H), 7.18–7.11 (m, 2H), 4.72 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.16 (d, 1H, J = 14.1 Hz), 3.81 (sep, 1H, J = 6.7 Hz), 3.79 (d, 1H, J = 14.1 Hz), 1.93 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.15 (d, 3H, J = 6.7 Hz), 1.07 (d, 3H, J = 6.7 Hz), 1.06 (d, 3H, J = 6.7 Hz).
107		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.85 (s, 1H), 8.43 (s, 1H), 7.69 (s, 1H), 7.37–7.29 (m, 2H), 7.19–7.11 (m, 2H), 4.73 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.12 (d, 1H, J = 14.1 Hz), 3.79 (d, 1H, J = 14.1 Hz), 2.93 (s, 6H), 1.98 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz).

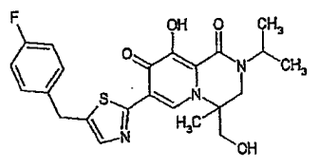
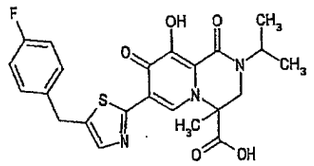
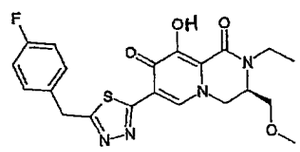
[0445]

[Table 1-29]

No.	structural formula	salt	^{1}H-NMR
108		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.96 (br s, 1H), 8.39 (s, 1H), 7.69 (s, 1H), 7.37-7.30 (m, 2H), 7.19-7.11 (m, 2H), 4.75 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.03 (d, 1H, J = 14.4 Hz), 3.80 (d, 1H, J = 14.4 Hz), 3.56-3.37 (br m, 4H), 1.90 (s, 3H), 1.59-1.50 (br m, 2H), 1.50-1.41 (br m, 4H), 1.18 (d, 3H, J = 6.7 Hz), 1.14 (d, 3H, J = 6.7 Hz).
109		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.79 (br s, 1H), 8.54 (s, 1H), 7.69 (s, 1H), 7.37-7.30 (m, 2H), 7.19-7.11 (m, 2H), 4.70 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.12 (d, 1H, J = 14.1 Hz), 3.75 (d, 1H, J = 14.1 Hz), 3.65-3.53 (br m, 1H), 3.43-3.33 (br m, 1H), 3.33-3.23 (br m, 1H), 3.16-3.05 (br m, 1H), 2.01 (s, 3H), 1.94-1.84 (br m, 1H), 1.81-1.56 (br m, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.7 Hz).
110		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.12 (s, 1H), 8.63 (s, 1H), 7.69 (s, 1H), 7.36-7.30 (m, 2H), 7.18-7.11 (m, 2H), 4.79 (sep, 1H, J = 6.7 Hz), 4.20 (s, 2H), 3.74 (d, 1H, J = 10.2 Hz), 3.73 (d, 1H, J = 13.9 Hz), 3.66 (d, 1H, J = 10.2 Hz), 3.65 (d, 1H, J = 13.9 Hz), 3.54-3.42 (m, 2H), 3.38-3.30 (m, 2H), 3.11 (s, 3H), 1.63 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz).

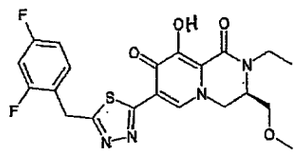
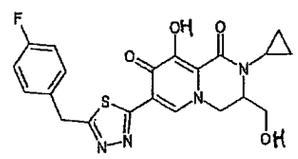
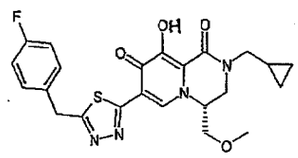
[0446]

[Table 1-30]

No.	structural formula	salt	^{1}H-NMR
111		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.14 (s, 1H), 8.63 (s, 1H), 7.69 (s, 1H), 7.36–7.30 (m, 2H), 7.18–7.11 (m, 2H), 4.79 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 3.72 (d, 1H, J = 13.7 Hz), 3.64 (d, 1H, J = 13.7 Hz), 3.61 (s, 2H), 1.59 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz).
112		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.87 (br s, 1H), 8.61 (s, 1H), 7.70 (s, 1H), 7.37–7.30 (m, 2H), 7.18–7.11 (m, 2H), 4.73 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.06 (d, 1H, J = 13.7 Hz), 3.80 (d, 1H, J = 13.7 Hz), 1.98 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.14 (d, 3H, J = 6.7 Hz).
113		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.64–12.34 (m, 1H), 8.83 (s, 1H), 7.44–7.37 (m, 2H), 7.22–7.14 (m, 2H), 4.64 (dd, 1H, J = 13.4, 1.5 Hz), 4.47 (s, 2H), 4.42 (dd, 1H, J = 13.4, 4.4 Hz), 4.17–4.11 (m, 1H), 3.86 (dq, 1H, J = 14.0, 7.0 Hz), 3.54 (dd, 1H, J = 10.4, 4.9 Hz), 3.50 (dd, 1H, J = 10.4, 6.3 Hz), 3.27 (dq, 1H, J = 14.0, 7.0 Hz), 3.22 (s, 3H), 1.20 (t, 3H, J = 7.0 Hz).

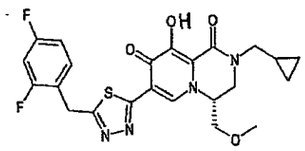
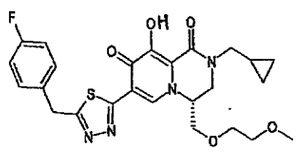
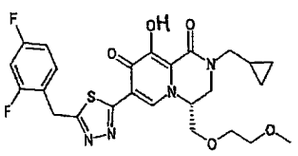
[0447]

[Table 1-31]

No.	structural formula	salt	^{1}H-NMR
114		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.50 (br s, 1H), 8.83 (s, 1H), 7.57–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.64 (dd, 1H, J = 13.7, 1.6 Hz), 4.49 (s, 2H), 4.43 (dd, 1H, J = 13.7, 4.1 Hz), 4.17–4.12 (m, 1H), 3.86 (dq, 1H, J = 13.4, 7.0 Hz), 3.54 (dd, 1H, J = 10.2, 5.1 Hz), 3.50 (dd, 1H, J = 10.2, 6.3 Hz), 3.27 (dq, 1H, J = 13.4, 7.0 Hz), 3.21 (s, 3H), 1.18 (t, 3H, J = 7.0 Hz).
115		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.72 (br s, 1H), 8.79 (s, 1H), 7.44–7.37 (m, 2H), 7.22–7.15 (m, 2H), 4.61 (dd, 1H, J = 13.6, 1.6 Hz), 4.47 (s, 2H), 4.35 (dd, 1H, J = 13.6, 4.2 Hz), 3.86–3.80 (m, 1H), 3.62 (dd, 1H, J = 11.5, 3.8 Hz), 3.52 (dd, 1H, J = 11.5, 7.1 Hz), 2.95–2.88 (m, 1H), 1.03–0.94 (m, 1H), 0.90–0.83 (m, 1H), 0.83–0.72 (m, 2H).
116		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.75 (s, 1H), 8.79 (s, 1H), 7.46–7.38 (m, 2H), 7.24–7.15 (m, 2H), 5.02–4.90 (m, 1H), 4.47 (s, 2H), 4.12 (dd, 1H, J = 13.7, 3.9 Hz), 3.87–3.79 (m, 1H), 3.73–3.58 (m, 2H), 3.45 (dd, 1H, J = 14.0, 7.3 Hz), 3.31 (dd, 1H, J = 14.0, 6.8 Hz), 3.26 (s, 3H), 1.15–1.03 (m, 1H), 0.58–0.46 (m, 2H), 0.39–0.26 (m, 2H).

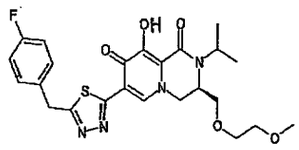
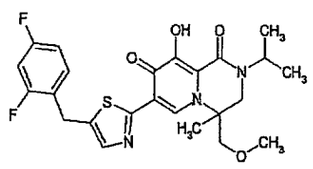
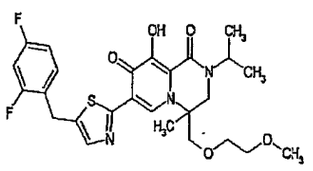
[0448]

[Table 1-32]

No.	structural formula	salt	^{1}H-NMR
117		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (br s, 1H), 8.79 (s, 1H), 7.59–7.50 (m, 1H), 7.33–7.26 (m, 1H), 7.15–7.08 (m, 1H), 4.99–4.92 (m, 1H), 4.49 (s, 2H), 4.12 (dd, 1H, J = 13.8, 4.3 Hz), 3.87–3.80 (m, 1H), 3.69 (dd, 1H, J = 10.4, 5.6 Hz), 3.62 (dd, 1H, J = 10.4, 7.9 Hz), 3.45 (dd, 1H, J = 13.8, 7.3 Hz), 3.31 (dd, 1H, J = 13.9, 7.0 Hz), 3.26 (s, 3H), 1.14–1.03 (m, 1H), 0.57–0.46 (m, 2H), 0.39–0.27 (m, 2H).
118		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.76 (s, 1H), 8.80 (s, 1H), 7.45–7.38 (m, 2H), 7.23–7.15 (m, 2H), 4.96–4.89 (m, 1H), 4.47 (s, 2H), 4.11 (dd, 1H, J = 13.7, 4.2 Hz), 3.84 (dd, 1H, J = 13.7, 1.2 Hz), 3.78 (dd, 1H, J = 10.5, 5.6 Hz), 3.70 (dd, 1H, J = 10.5, 7.7 Hz), 3.59–3.39 (m, 3H), 3.37–3.29 (m, 3H), 3.10 (s, 3H), 1.13–1.04 (m, 1H), 0.58–0.46 (m, 2H), 0.38–0.27 (m, 2H).
119		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (br s, 1H), 8.80 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.16–7.08 (m, 1H), 4.97–4.89 (m, 1H), 4.49 (s, 2H), 4.12 (dd, 1H, J = 13.7, 4.4 Hz), 3.84 (dd, 1H, J = 13.7, 1.2 Hz), 3.78 (dd, 1H, J = 10.5, 5.6 Hz), 3.70 (dd, 1H, J = 10.5, 7.7 Hz), 3.59–3.40 (m, 3H), 3.37–3.29 (m, 3H), 3.10 (s, 3H), 1.14–1.04 (m, 1H), 0.58–0.47 (m, 2H), 0.38–0.27 (m, 2H).

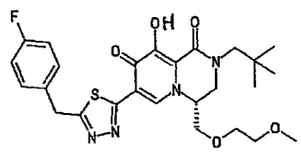
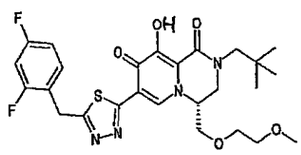
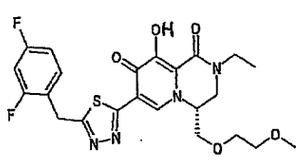
[0449]

[Table 1-33]

No.	structural formula	salt	^{1}H-NMR
120		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.42 (br s, 1H), 8.82 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.14 (m, 2H), 4.65 (d, 1H, J = 12.5 Hz), 4.55-4.42 (m, 1H), 4.47 (s, 2H), 4.36 (dd, 1H, J = 13.1, 3.6 Hz), 4.23-4.13 (m, 1H), 3.52-3.39 (m, 4H), 3.32-3.25 (m, 2H), 3.09 (s, 3H), 1.29 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).
121		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.10 (br s, 1H), 8.58 (s, 1H), 7.66 (s, 1H), 7.44 (td, 1H, J = 8.7, 6.7 Hz), 7.23 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.06 (tdd, 1H, J = 8.7, 2.6, 0.9 Hz), 4.78 (sep, 1H, J = 6.7 Hz), 4.20 (s, 2H), 3.73 (d, 1H, J = 13.9 Hz), 3.63 (d, 1H, J = 13.9 Hz), 3.63 (d, 1H, J = 10.2 Hz), 3.56 (d, 1H, J = 10.2 Hz), 3.22 (s, 3H), 1.61 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
122		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.12 (br s, 1H), 8.62 (s, 1H), 7.67 (s, 1H), 7.45 (td, 1H, J = 8.8, 7.0 Hz), 7.25 (ddd, 1H, J = 10.4, 9.3, 2.6 Hz), 7.07 (tdd, 1H, J = 8.8, 2.6, 1.0 Hz), 4.79 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 3.78-3.70 (m, 2H), 3.66 (d, 1H, J = 10.2 Hz), 3.65 (d, 1H, J = 13.9 Hz), 3.54-3.42 (m, 2H), 3.37-3.29 (m, 2H), 3.11 (s, 3H), 1.63 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz).

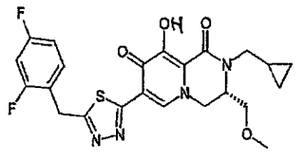
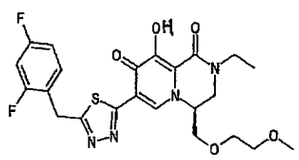
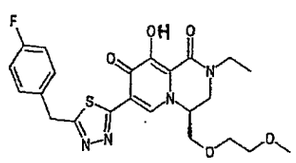
[0450]

[Table 1-34]

No.	structural formula	salt	^{1}H-NMR
123		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.78 (s, 1H), 8.82 (s, 1H), 7.45-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.93-4.86 (m, 1H), 4.47 (s, 2H), 4.19 (dd, 1H, J = 13.7, 4.2 Hz), 3.82 (dd, 1H, J = 10.4, 5.6 Hz), 3.78-3.70 (m, 2H), 3.58-3.47 (m, 2H), 3.42 (d, 1H, J = 13.4 Hz), 3.35-3.31 (m, 2H), 3.23 (d, 1H, J = 13.4 Hz), 3.11 (s, 3H), 0.98 (s, 9H).
124		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.78 (br s, 1H), 8.80 (s, 1H), 7.57-7.50 (m, 1H), 7.32-7.24 (m, 1H), 7.14-7.07 (m, 1H), 4.92-4.85 (m, 1H), 4.48 (s, 2H), 4.18 (dd, 1H, J = 13.7, 4.2 Hz), 3.81 (dd, 1H, J = 10.6, 5.7 Hz), 3.76-3.69 (m, 2H), 3.56-3.46 (m, 2H), 3.41 (d, 1H, J = 13.4 Hz), 3.34-3.30 (m, 2H), 3.22 (d, 1H, J = 13.4 Hz), 3.09 (s, 3H), 0.97 (s, 9H).
125		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.78 (br s, 1H), 8.79 (s, 1H), 7.58-7.50 (m, 1H), 7.33-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.96-4.88 (m, 1H), 4.49 (s, 2H), 4.07 (dd, 1H, J = 13.6, 4.3 Hz), 3.79-3.59 (m, 4H), 3.57-3.45 (m, 2H), 3.45-3.36 (m, 1H), 3.33 (t, 2H, J = 4.6 Hz), 3.10 (s, 3H), 1.15 (t, 3H, J = 7.2 Hz).

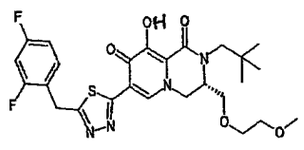
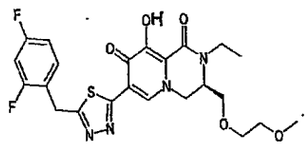
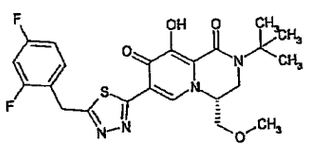
[0451]

[Table 1-35]

No.	structural formula	salt	^{1}H-NMR
126		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.47 (br s, 1H), 8.83 (s, 1H), 7.56–7.49 (m, 1H), 7.32–7.24 (m, 1H), 7.14–7.07 (m, 1H), 4.66 (dd, 1H, J = 13.4, 1.6 Hz), 4.48 (s, 2H), 4.44 (dd, 1H, J = 13.4, 4.2 Hz), 4.25–4.20 (m, 1H), 3.68 (dd, 1H, J = 14.0, 7.0 Hz), 3.57 (dd, 1H, J = 10.2, 4.6 Hz), 3.50 (dd, 1H, J = 10.2, 6.5 Hz), 3.20 (dd, 1H, J = 14.0, 7.0 Hz), 3.20 (s, 3H), 1.20–1.09 (m, 1H), 0.58–0.46 (m, 2H), 0.43–0.35 (m, 1H), 0.35–0.27 (m, 1H).
127		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.78 (br s, 1H), 8.79 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.96–4.88 (m, 1H), 4.49 (s, 2H), 4.07 (dd, 1H, J = 13.6, 4.3 Hz), 3.79–3.59 (m, 4H), 3.57–3.45 (m, 2H), 3.45–3.36 (m, 1H), 3.33 (t, 2H, J = 4.6 Hz), 3.10 (s, 3H), 1.15 (t, 3H, J = 7.2 Hz).
128		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (br s, 1H), 8.80 (s, 1H), 7.44–7.39 (m, 2H), 7.22–7.15 (m, 2H), 4.95–4.88 (m, 1H), 4.47 (s, 2H), 4.07 (dd, 1H, J = 13.6, 4.3 Hz), 3.78–3.60 (m, 4H), 3.57–3.46 (m, 2H), 3.43–3.37 (m, 1H), 3.33 (t, 2H, J = 4.6 Hz), 3.10 (s, 3H), 1.15 (t, 3H, J = 7.2 Hz).

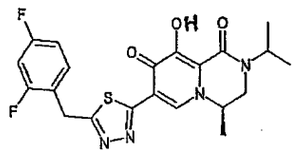
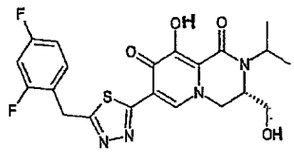
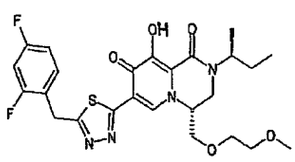
[0452]

[Table 1-36]

No.	structural formula	salt	^{1}H-NMR
129		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.67 (s, 1H), 8.83 (s, 1H), 7.59–7.49 (m, 1H), 7.34–7.25 (m, 1H), 7.16–7.07 (m, 1H), 4.70–4.55 (m, 2H), 4.49 (s, 2H), 4.03–3.97 (br m, 1H), 3.95 (d, 1H, J = 13.4 Hz), 3.66–3.59 (m, 2H), 3.47–3.41 (m, 2H), 3.27–3.22 (m, 2H), 3.07 (s, 3H), 2.85 (d, 1H, J = 13.4 Hz), 0.98 (s, 9H).
130		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.50 (s, 1H), 8.80 (s, 1H), 7.59–7.49 (m, 1H), 7.34–7.25 (m, 1H), 7.15–7.07 (m, 1H), 4.68–4.59 (m, 1H), 4.48 (s, 2H), 4.43 (dd, 1H, J = 13.4, 4.2 Hz), 4.17–4.09 (m, 1H), 3.86 (td, 1H, J = 13.9, 7.0 Hz), 3.67–3.56 (m, 2H), 3.52–3.41 (m, 2H), 3.34–3.22 (m, 3H), 3.09 (s, 3H), 1.20 (t, 3H, J = 7.0 Hz).
131		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.97–12.84 (br m, 1H), 8.76 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.92–4.85 (br m, 1H), 4.48 (s, 2H), 3.98–3.84 (m, 2H), 3.67 (dd, 1H, J = 10.1, 5.6 Hz), 3.59 (dd, 1H, J = 10.1, 7.7 Hz), 3.28 (s, 3H), 1.48 (s, 9H).

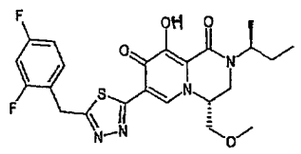
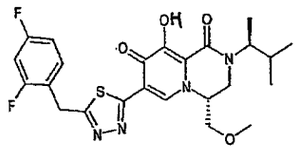
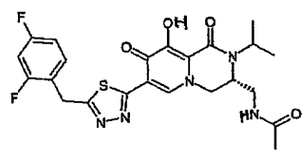
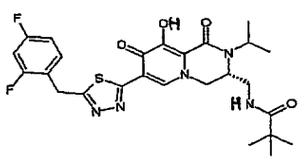
[0453]

[Table 1-37]

No.	structural formula	salt	^{1}H-NMR
132		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.79 (br s, 1H), 8.90 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.97–4.88 (m, 1H), 4.84–4.74 (m, 1H), 4.49 (s, 2H), 3.81 (dd, 1H, J = 13.5, 3.7 Hz), 3.63 (dd, 1H, J = 13.5, 2.2 Hz), 1.39 (d, 3H, J = 6.6 Hz), 1.19 (d, 3H, J = 6.8 Hz), 1.16 (d, 3H, J = 6.8 Hz).
133		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.48 (s, 1H), 8.80 (s, 1H), 7.57–7.50 (m, 1H), 7.32–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.67 (d, 1H, J = 13.1 Hz), 4.51 (sep, 1H, J = 6.8 Hz), 4.49 (s, 2H), 4.34 (dd, 1H, J = 13.1, 3.7 Hz), 4.00–3.93 (m, 1H), 3.57 (dd, 1H, J = 11.4, 3.7 Hz), 3.37 (dd, 1H, J = 11.4, 8.3 Hz), 1.29 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).
134		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.88 (br s, 1H), 8.83–8.80 (m, 1H), 7.59–7.50 (m, 1H), 7.33–7.24 (m, 1H), 7.16–7.08 (m, 1H), 5.01–4.90 (br m, 1H), 4.60–4.50 (m, 1H), 4.49 (s, 2H), 3.87–3.63 (m, 4H), 3.57–3.46 (m, 2H), 3.35–3.30 (m, 2H), 3.12–3.10 (m, 3H), 1.59–1.48 (m, 2H), 1.15 (d, 3H, J = 6.7 Hz), 0.91–0.78 (m, 3H).

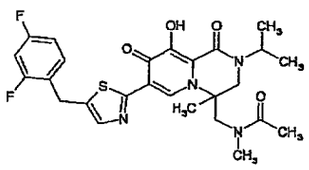
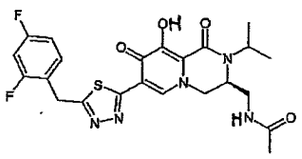
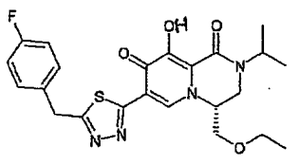
[0454]

[Table 1-38]

No.	structural formula	salt	^{1}H-NMR
135		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.89 (br s, 1H), 8.81 (s, 1H), 7.59–7.50 (m, 1H), 7.34–7.25 (m, 1H), 7.16–7.06 (m, 1H), 5.03–4.92 (br m, 1H), 4.59–4.50 (m, 1H), 4.49 (s, 2H), 3.73–3.54 (m, 4H), 3.26–3.23 (m, 3H), 1.61–1.45 (m, 2H), 1.15 (d, 3H, J = 6.7 Hz), 0.91–0.80 (m, 3H).
136		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.96 (br s, 1H), 8.82 (s, 1H), 7.59–7.49 (m, 1H), 7.35–7.24 (m, 1H), 7.17–7.06 (m, 1H), 5.04–4.91 (m, 1H), 4.49 (s, 2H), 4.30–3.57 (m, 5H), 3.27–3.22 (m, 3H), 1.87–1.69 (m, 1H), 1.17 (d, 3H, J = 6.8 Hz), 0.97–0.79 (m, 6H).
137		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.42 (br s, 1H), 8.71 (s, 1H), 8.23–8.17 (m, 1H), 7.58–7.50 (m, 1H), 7.33–7.26 (m, 1H), 7.15–7.08 (m, 1H), 4.58 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.43 (dd, 1H, J = 13.0, 1.3 Hz), 4.31 (dd, 1H, J = 13.0, 3.0 Hz), 3.97–3.91 (m, 1H), 3.45–3.36 (m, 1H), 2.97–2.86 (m, 1H), 1.80 (s, 3H), 1.34 (d, 3H, J = 6.7 Hz), 1.27 (d, 3H, J = 6.7 Hz).
138		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.49 (br s, 1H), 8.72 (s, 1H), 7.88–7.83 (m, 1H), 7.57–7.50 (m, 1H), 7.32–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.57 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.38–4.28 (m, 2H), 3.99–3.92 (m, 1H), 3.38–3.29 (m, 1H), 3.04–2.95 (m, 1H), 1.38 (d, 3H, J = 6.7 Hz), 1.29 (d, 3H, J = 6.7 Hz), 1.08 (s, 9H).

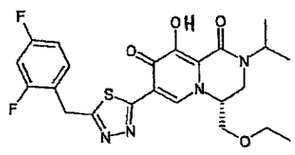
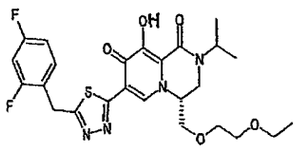
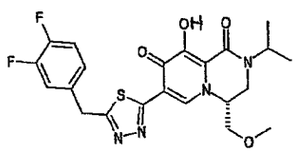
[0455]

[Table 1-39]

No.	structural formula	salt	^{1}H-NMR
139		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.18 (br s, 1H), 8.47 (s, 1H), 7.67 (s, 1H), 7.46 (td, 1H, J = 8.8, 6.6 Hz), 7.25 (ddd, 1H, J = 10.4, 9.3, 2.6 Hz), 7.08 (tdd, 1H, J = 8.8, 2.6, 0.9 Hz), 4.79 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 3.79 (d, 1H, J = 13.9 Hz), 3.74 (d, 1H, J = 14.6 Hz), 3.68 (d, 1H, J = 13.9 Hz), 3.57 (d, 1H, J = 14.6 Hz), 2.75 (s, 3H), 1.81 (s, 3H), 1.67 (s, 3H), 1.22 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz).
140		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.42 (br s, 1H), 8.71 (s, 1H), 8.22–8.17 (m, 1H), 7.57–7.50 (m, 1H), 7.33–7.26 (m, 1H), 7.15–7.08 (m, 1H), 4.58 (sep, 1H, J = 6.8 Hz), 4.49 (s, 2H), 4.43 (d, 1H, J = 13.0 Hz), 4.30 (dd, 1H, J = 13.0, 3.0 Hz), 3.98–3.91 (m, 1H), 2.96–2.86 (m, 1H), 2.56–2.50 (m, 1H), 1.80 (s, 3H), 1.34 (d, 3H, J = 6.8 Hz), 1.27 (d, 3H, J = 6.8 Hz).
141		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.84 (s, 1H), 8.82 (s, 1H), 7.45–7.38 (m, 2H), 7.23–7.15 (m, 2H), 4.99–4.91 (m, 1H), 4.77 (sep, 1H, J = 6.8 Hz), 4.47 (s, 2H), 3.84 (dd, 1H, J = 13.8, 4.1 Hz), 3.75 (dd, 1H, J = 13.8, 1.7 Hz), 3.66 (dd, 1H, J = 10.4, 6.0 Hz), 3.59 (dd, 1H, J = 10.4, 7.5 Hz), 3.50–3.34 (m, 2H), 1.17 (d, 3H, J = 6.8 Hz), 1.16 (d, 3H, J = 6.8 Hz), 1.02 (t, 3H, J = 7.1 Hz).

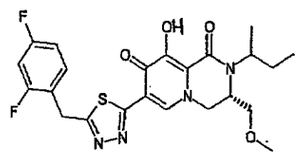
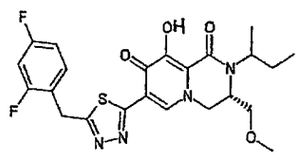
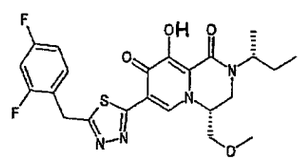
[0456]

[Table 1-40]

No.	structural formula	salt	^{1}H-NMR
142		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.81 (s, 1H), 7.58–7.51 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.07 (m, 1H), 4.98–4.91 (m, 1H), 4.77 (sep, 1H, J = 6.8 Hz), 4.49 (s, 2H), 3.84 (dd, 1H, J = 13.7, 4.0 Hz), 3.78–3.73 (m, 1H), 3.69–3.56 (m, 2H), 3.50–3.34 (m, 2H), 1.17 (d, 3H, J = 6.8 Hz), 1.16 (d, 3H, J = 6.8 Hz), 1.02 (t, 3H, J = 7.1 Hz).
143		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.85 (br s, 1H), 8.80 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.99–4.92 (m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 3.84 (dd, 1H, J = 13.8, 4.1 Hz), 3.79–3.68 (m, 2H), 3.65 (dd, 1H, J = 10.4, 7.9 Hz), 3.56–3.44 (m, 2H), 3.38–3.34 (m, 2H), 3.30–3.22 (m, 2H), 1.17 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz), 0.91 (t, 3H, J = 7.0 Hz).
144		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.82 (br s, 1H), 8.81 (s, 1H), 7.52–7.38 (m, 2H), 7.26–7.21 (m, 1H), 5.00–4.94 (m, 1H), 4.77 (sep, 1H, J = 6.9 Hz), 4.49 (s, 2H), 3.84 (dd, 1H, J = 13.7, 4.0 Hz), 3.75 (dd, 1H, J = 13.7, 1.2 Hz), 3.66–3.54 (m, 2H), 3.25 (s, 3H), 1.16 (d, 3H, J = 6.9 Hz), 1.16 (d, 3H, J = 6.9 Hz).

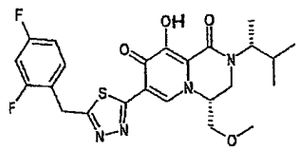
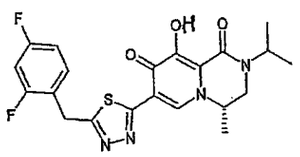
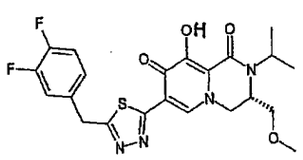
[0457]

[Table 1-41]

No.	structural formula	salt	^{1}H-NMR
145		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.45 (br s, 1H), 8.85 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.71–4.65 (m, 1H), 4.49 (s, 2H), 4.38–4.27 (m, 2H), 4.17–4.11 (m, 1H), 3.50 (dd, 1H, J = 10.5, 4.1 Hz), 3.39 (dd, 1H, J = 10.5, 7.7 Hz), 3.20 (s, 3H), 1.78–1.59 (m, 2H), 1.25 (d, 3H, J = 6.8 Hz), 0.86 (t, 3H, J = 7.4 Hz).
146		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.48 (br s, 1H), 8.83 (s, 1H), 7.57–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.65 (dd, 1H, J = 13.5, 1.1 Hz), 4.49 (s, 2H), 4.38 (dd, 1H, J = 13.5, 4.1 Hz), 4.15–4.03 (m, 2H), 3.50 (dd, 1H, J = 10.1, 4.2 Hz), 3.42 (dd, 1H, J = 10.1, 7.1 Hz), 3.20 (s, 3H), 1.83–1.73 (m, 1H), 1.63–1.53 (m, 1H), 1.33 (d, 3H, J = 6.8 Hz), 0.91 (t, 3H, J = 7.4 Hz).
147		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.85 (br s, 1H), 8.81 (s, 1H), 7.59–7.49 (m, 1H), 7.33–7.25 (m, 1H), 7.16–7.08 (m, 1H), 5.05–4.86 (br m, 1H), 4.60–4.50 (m, 1H), 4.49 (s, 2H), 3.87–3.56 (m, 4H), 3.25–3.25 (m, 3H), 1.54–1.50 (m, 2H), 1.15 (d, 3H, J = 6.5 Hz), 0.91–0.80 (m, 3H).

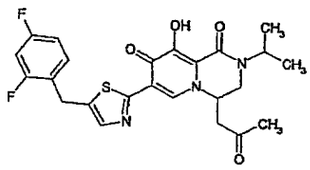
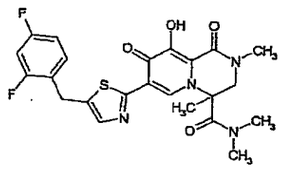
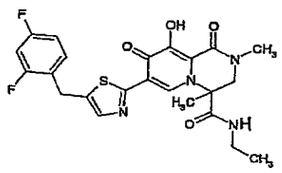
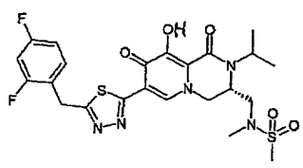
[0458]

[Table 1-42]

No.	structural formula	salt	^{1}H-NMR
148		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.87 (br s, 1H), 8.81 (s, 1H), 7.58–7.52 (m, 1H), 7.32–7.27 (m, 1H), 7.16–7.07 (m, 1H), 5.05–4.90 (m, 1H), 4.49 (s, 2H), 4.32–4.20 (m, 1H), 3.90–3.57 (m, 4H), 3.26–3.24 (m, 3H), 1.87–1.69 (m, 1H), 1.19–1.10 (m, 3H), 0.97–0.79 (m, 6H).
149		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.79 (br s, 1H), 8.90 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.97–4.88 (m, 1H), 4.84–4.74 (m, 1H), 4.49 (s, 2H), 3.81 (dd, 1H, J = 13.5, 3.7 Hz), 3.63 (dd, 1H, J = 13.5, 2.2 Hz), 1.39 (d, 3H, J = 6.6 Hz), 1.19 (d, 3H, J = 6.8 Hz), 1.16 (d, 3H, J = 6.8 Hz).
150		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.44 (br s, 1H), 8.85 (s, 1H), 7.53–7.37 (m, 2H), 7.26–7.19 (m, 1H), 4.66 (dd, 1H, J = 13.5, 1.5 Hz), 4.51–4.43 (m, 1H), 4.49 (s, 2H), 4.38–4.32 (m, 1H), 4.23–4.17 (m, 1H), 3.49 (dd, 1H, J = 10.4, 4.4 Hz), 3.39 (dd, 1H, J = 10.4, 7.5 Hz), 3.22 (s, 3H), 1.30 (d, 3H, J = 6.6 Hz), 1.29 (d, 3H, J = 6.8 Hz).

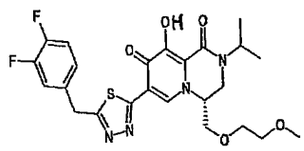
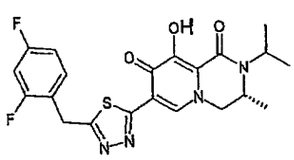
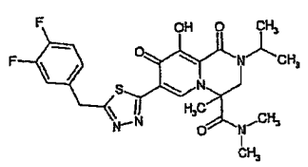
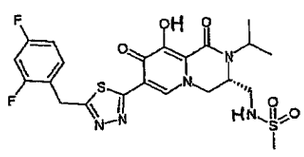
[0459]

[Table 1-43]

No.	structural formula	salt	^{1}H-NMR
151		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.86-12.34 (m, 1H), 8.68 (s, 1H), 7.66 (s, 1H), 7.49-7.39 (m, 1H), 7.29-7.20 (m, 1H), 7.11-7.02 (m, 1H), 5.12-5.03 (m, 1H), 4.84-4.70 (m, 1H), 4.21 (s, 2H), 3.82-3.55 (m, 2H), 3.15-2.96 (m, 2H), 2.08 (s, 3H), 1.17-1.09 (m, 6H).
152		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.77 (br s, 1H), 8.43 (s, 1H), 7.68 (s, 1H), 7.50-7.41 (m, 1H), 7.29-7.20 (m, 1H), 7.11-7.03 (m, 1H), 4.24-4.16 (m, 1H), 4.22 (s, 2H), 3.91 (d, 1H, J = 13.9 Hz), 3.07 (s, 3H), 2.89 (s, 6H), 1.92 (s, 3H).
153		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.64 (br s, 1H), 8.53 (s, 1H), 8.34-8.23 (m, 1H), 7.68 (s, 1H), 7.50-7.40 (m, 1H), 7.30-7.20 (m, 1H), 7.13-7.02 (m, 1H), 4.23 (s, 2H), 4.12 (d, 1H, J = 14.1 Hz), 4.01 (d, 1H, J = 14.1 Hz), 3.17-2.97 (m, 2H), 3.03 (s, 3H), 1.87 (s, 3H), 0.99 (t, 3H, J = 7.4 Hz).
154		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.32 (s, 1H), 8.79 (s, 1H), 7.58-7.50 (m, 1H), 7.32-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.60 (d, 1H, J = 13.0 Hz), 4.55 (sep, 1H, J = 6.8 Hz), 4.48 (s, 2H), 4.35 (dd, 1H, J = 13.0, 3.0 Hz), 4.27-4.20 (m, 1H), 3.26 (dd, 1H, J = 13.7, 10.5 Hz), 2.99 (dd, 1H, J = 13.7, 3.0 Hz), 2.87 (s, 3H), 2.84 (s, 3H), 1.30 (d, 6H, J = 6.8 Hz).

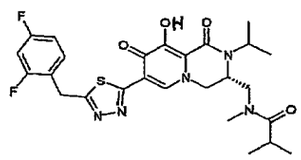
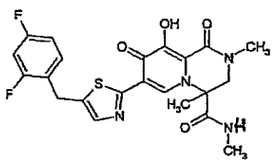
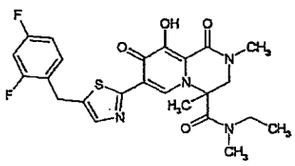
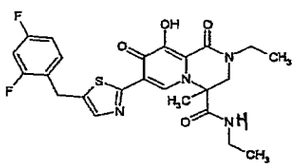
[0460]

[Table 1-44]

No.	structural formula	salt	^{1}H-NMR
155		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.82 (s, 1H), 7.52–7.37 (m, 2H), 7.27–7.20 (m, 1H), 4.99–4.91 (m, 1H), 4.77 (sep, 1H, J = 6.9 Hz), 4.49 (s, 2H), 3.84 (dd, 1H, J = 13.7, 4.0 Hz), 3.79–3.69 (m, 2H), 3.64 (dd, 1H, J = 10.5, 7.7 Hz), 3.58–3.45 (m, 2H), 3.34 (t, 2H, J = 4.6 Hz), 3.11 (s, 3H), 1.17 (d, 3H, J = 6.9 Hz), 1.16 (d, 3H, J = 6.9 Hz).
156		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.84 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.62–4.53 (m, 1H), 4.51–4.45 (m, 3H), 4.32 (dd, 1H, J = 13.1, 3.4 Hz), 4.26–4.18 (m, 1H), 1.27 (d, 3H, J = 6.9 Hz), 1.26 (d, 3H, J = 6.9 Hz), 1.21 (d, 3H, J = 6.4 Hz).
157		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.96 (s, 1H), 8.56 (s, 1H), 7.53–7.19 (m, 3H), 4.80–4.66 (m, 1H), 4.50 (s, 2H), 4.15 (d, 1H, J = 14.3 Hz), 3.82 (d, 1H, J = 14.3 Hz), 3.09–2.83 (m, 6H), 2.04 (s, 3H), 1.18 (d, 3H, J = 7.1 Hz), 1.11 (d, 3H, J = 7.1 Hz).
158		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.35 (s, 1H), 8.75 (s, 1H), 7.57–7.49 (m, 2H), 7.32–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.61–4.53 (m, 2H), 4.49 (s, 2H), 4.40–4.33 (m, 1H), 4.00–3.93 (m, 1H), 3.21–3.12 (m, 1H), 3.02–2.92 (m, 1H), 2.90 (s, 3H), 1.30 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).

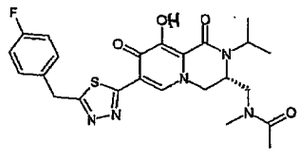
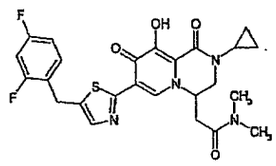
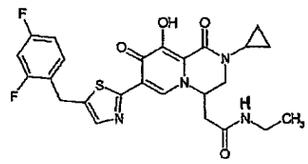
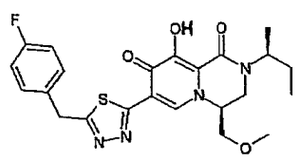
[0461]

[Table 1-45]

No.	structural formula	salt	^{1}H-NMR
159		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.39 (br s, 1H), 8.83 (s, 1H), 7.58-7.49 (m, 1H), 7.32-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.56 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.42-4.28 (m, 2H), 4.26-4.18 (m, 1H), 3.41-3.36 (m, 2H), 3.04 (s, 3H), 2.83 (t, 1H, J = 6.7 Hz), 1.34 (d, 3H, J = 6.7 Hz), 1.29 (d, 3H, J = 6.7 Hz), 1.00 (d, 3H, J = 6.7 Hz), 0.99 (d, 3H, J = 6.7 Hz).
160		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.67 (br s, 1H), 8.53 (s, 1H), 8.12-8.02 (m, 1H), 7.67 (s, 1H), 7.49-7.40 (m, 1H), 7.29-7.20 (m, 1H), 7.12-7.02 (m, 1H), 4.22 (s, 2H), 4.07 (d, 1H, J = 14.1 Hz), 3.99 (d, 1H, J = 14.1 Hz), 3.03 (s, 3H), 2.60 (d, 3H, J = 4.6 Hz), 1.86 (s, 3H).
161		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.76 (br s, 1H), 8.41 (s, 1H), 7.66 (s, 1H), 7.50-7.40 (m, 1H), 7.29-7.20 (m, 1H), 7.12-7.03 (m, 1H), 4.22 (s, 2H), 4.17 (d, 1H, J = 13.9 Hz), 3.91 (d, 1H, J = 13.9 Hz), 3.46-3.17 (m, 2H), 3.06 (s, 3H), 2.84 (s, 3H), 1.90 (s, 3H), 0.99 (t, 3H, J = 7.4 Hz).
162		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.71 (br s, 1H), 8.52 (s, 1H), 8.31-8.22 (m, 1H), 7.67 (s, 1H), 7.50-7.39 (m, 1H), 7.31-7.19 (m, 1H), 7.13-7.03 (m, 1H), 4.22 (s, 2H), 4.14 (d, 1H, J = 13.7 Hz), 3.99 (d, 1H, J = 13.7 Hz), 3.66-3.28 (m, 2H), 3.15-3.00 (m, 2H), 1.89 (s, 3H), 1.11 (t, 3H, J = 7.4 Hz), 0.99 (t, 3H, J = 7.4 Hz).

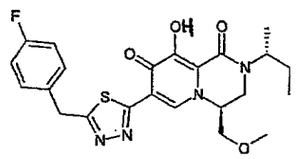
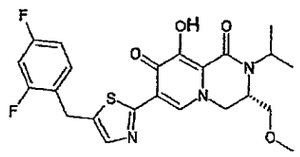
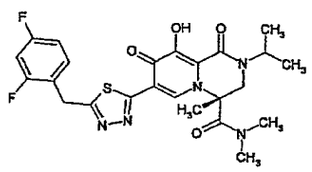
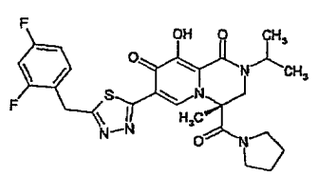
[0462]

[Table 1-46]

No.	structural formula	salt	^{1}H-NMR
163		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.34 (br s, 1H), 8.78 (s, 1H), 7.44–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.55 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 4.43 (d, 1H, J = 12.4 Hz), 4.38–4.27 (m, 1H), 4.25–4.17 (m, 1H), 3.44 (dd, 1H, J = 13.3, 10.0 Hz), 3.34–3.28 (m, 1H), 3.00 (s, 3H), 1.99 (s, 3H), 1.33 (d, 3H, J = 6.7 Hz), 1.29 (d, 3H, J = 6.7 Hz).
164		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.71 (s, 1H), 7.66 (s, 1H), 7.49–7.40 (m, 1H), 7.29–7.20 (m, 1H), 7.12–7.03 (m, 1H), 5.06–4.95 (m, 1H), 4.21 (s, 2H), 4.04 (dd, 1H, J = 13.4, 3.5 Hz), 3.68–3.60 (m, 1H), 2.97–2.88 (m, 1H), 2.88–2.82 (m, 2H), 2.87 (s, 3H), 2.79 (s, 3H), 0.96–0.83 (m, 2H), 0.83–0.72 (m, 1H), 0.67–0.55 (m, 1H).
165		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.52 (s, 1H), 7.99 (t, 1H, J = 4.9 Hz), 7.65 (s, 1H), 7.49–7.40 (m, 1H), 7.29–7.20 (m, 1H), 7.12–7.03 (m, 1H), 5.00–4.89 (m, 1H), 4.21 (s, 2H), 4.03 (dd, 1H, J = 13.9, 3.9 Hz), 3.58–3.50 (m, 1H), 3.03–2.83 (m, 3H), 2.56 (d, 2H, J = 7.4 Hz), 1.01–0.71 (m, 4H), 0.80 (t, 3H, J = 7.2 Hz).
166		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.81 (s, 1H), 7.47–7.36 (m, 2H), 7.23–7.12 (m, 2H), 5.04–4.91 (m, 1H), 4.60–4.49 (m, 1H), 4.47 (s, 2H), 3.88–3.54 (m, 4H), 3.27–3.23 (m, 3H), 1.61–1.46 (m, 2H), 1.15 (d, 3H, J = 6.4 Hz), 0.91–0.80 (m, 3H).

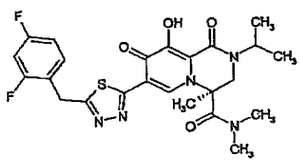
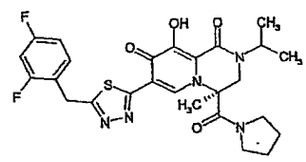
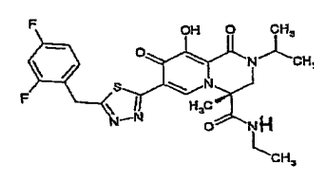
[0463]

[Table 1-47]

No.	structural formula	salt	^{1}H-NMR
167		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.81 (s, 1H), 7.46–7.38 (m, 2H), 7.23–7.14 (m, 2H), 5.02–4.92 (m, 1H), 4.60–4.49 (m, 1H), 4.47 (s, 2H), 3.89–3.54 (m, 4H), 3.27–3.23 (m, 3H), 1.59–1.47 (m, 2H), 1.15 (d, 3H, J = 6.4 Hz), 0.91–0.80 (m, 3H).
168		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.66 (s, 1H), 7.65 (s, 1H), 7.49–7.40 (m, 1H), 7.30–7.20 (m, 1H), 7.12–7.02 (m, 1H), 4.64–4.56 (m, 1H), 4.47 (sep, 1H, J = 6.7 Hz), 4.33 (dd, 1H, J = 13.3, 3.6 Hz), 4.24–4.14 (m, 3H), 3.48 (dd, 1H, J = 10.2, 4.2 Hz), 3.36 (dd, 1H, J = 10.2, 7.7 Hz), 3.21 (s, 3H), 1.29 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).
169		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.96 (br s, 1H), 8.55 (s, 1H), 7.54 (td, 1H, J = 8.6, 6.6 Hz), 7.29 (ddd, 1H, J = 10.2, 9.3, 2.6 Hz), 7.11 (tdd, 1H, J = 8.6, 2.6, 0.9 Hz), 4.73 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.15 (d, 1H, J = 14.4 Hz), 3.82 (d, 1H, J = 14.4 Hz), 2.95 (br s, 6H), 2.03 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz).
170		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.91 (br s, 1H), 8.64 (s, 1H), 7.54 (td, 1H, J = 8.8, 6.6 Hz), 7.29 (ddd, 1H, J = 10.4, 9.5, 2.8 Hz), 7.12 (tdd, 1H, J = 8.8, 2.8, 1.2 Hz), 4.70 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.14 (d, 1H, J = 14.1 Hz), 3.77 (d, 1H, J = 14.1 Hz), 3.71–3.50 (br m, 2H), 3.36–3.24 (br m, 1H), 3.21–3.08 (br m, 1H), 2.06 (s, 3H), 1.97–1.86 (br m, 1H), 1.83–1.59 (br m, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.7 Hz).

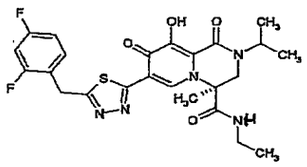
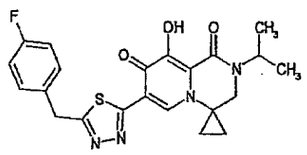
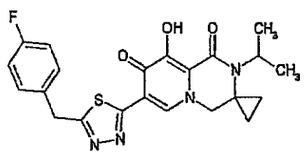
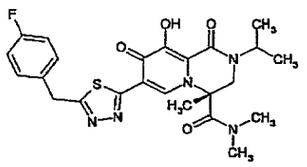
[0464]

[Table 1-48]

No.	structural formula	salt	^{1}H-NMR
171		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.96 (br s, 1H), 8.55 (s, 1H), 7.54 (td, 1H, J = 8.6, 6.6 Hz), 7.29 (ddd, 1H, J = 10.2, 9.3, 2.6 Hz), 7.11 (tdd, 1H, J = 8.6, 2.6, 0.9 Hz), 4.73 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.15 (d, 1H, J = 14.4 Hz), 3.82 (d, 1H, J = 14.4 Hz), 2.95 (br s, 6H), 2.03 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz).
172		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.91 (br s, 1H), 8.64 (s, 1H), 7.54 (td, 1H, J = 8.8, 6.6 Hz), 7.29 (ddd, 1H, J = 10.4, 9.5, 2.8 Hz), 7.12 (tdd, 1H, J = 8.8, 2.8, 1.2 Hz), 4.70 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.14 (d, 1H, J = 14.1 Hz), 3.77 (d, 1H, J = 14.1 Hz), 3.71–3.50 (br m, 2H), 3.36–3.24 (br m, 1H), 3.21–3.08 (br m, 1H), 2.06 (s, 3H), 1.97–1.86 (br m, 1H), 1.83–1.59 (br m, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.7 Hz).
173		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.93 (br s, 1H), 8.62 (s, 1H), 8.19 (t, 1H, J = 5.2 Hz), 7.54 (td, 1H, J = 8.7, 6.6 Hz), 7.29 (ddd, 1H, J = 10.4, 9.3, 2.6 Hz), 7.12 (tdd, 1H, J = 8.7, 2.6, 0.9 Hz), 4.71 (sep, 1H, J = 6.7 Hz), 4.50 (s, 2H), 4.11 (d, 1H, J = 13.9 Hz), 3.80 (d, 1H, J = 13.9 Hz), 3.18–2.98 (m, 2H), 1.96 (s, 3H), 1.15 (d, 3H, J = 6.7 Hz), 1.12 (d, 3H, J = 6.7 Hz), 1.00 (t, 3H, J = 7.2 Hz).

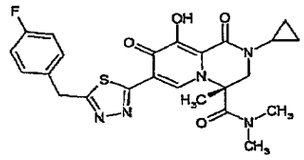
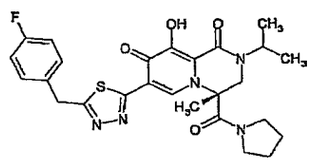
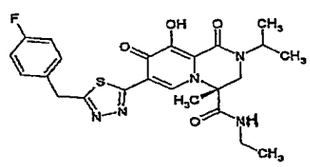
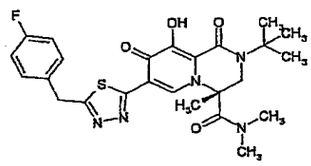
[0465]

[Table 1-49]

No.	structural formula	salt	^{1}H-NMR
174		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.93 (br s, 1H), 8.62 (s, 1H), 8.19 (t, 1H, J = 5.2 Hz), 7.54 (td, 1H, J = 8.7, 6.6 Hz), 7.29 (ddd, 1H, J = 10.4, 9.3, 2.6 Hz), 7.12 (tdd, 1H, J = 8.7, 2.6, 0.9 Hz), 4.71 (sep, 1H, J = 6.7 Hz), 4.50 (s, 2H), 4.11 (d, 1H, J = 13.9 Hz), 3.80 (d, 1H, J = 13.9 Hz), 3.18-2.98 (m, 2H), 1.96 (s, 3H), 1.15 (d, 3H, J = 6.7 Hz), 1.12 (d, 3H, J = 6.7 Hz), 1.00 (t, 3H, J = 7.2 Hz).
175		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.43 (s, 1H), 7.42-7.37 (m, 2H), 7.21-7.15 (m, 2H), 4.76 (sep, 1H, J = 6.9 Hz), 4.46 (s, 2H), 3.66 (s, 2H), 1.66-1.61 (m, 2H), 1.13-1.18 (m, 2H), 1.16 (d, 6H, J = 6.9 Hz).
176		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.67 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.47 (s, 2H), 4.31 (s, 2H), 4.15 (sep, 1H, J = 6.9 Hz), 1.35-1.29 (m, 2H), 1.32 (d, 6H, J = 6.9 Hz), 1.07-1.02 (m, 2H).
177		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.95 (s, 1H), 8.55 (s, 1H), 7.44-7.36 (m, 2H), 7.21-7.15 (m, 2H), 4.73 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.15 (d, 1H, J = 14.1 Hz), 3.82 (d, 1H, J = 14.1 Hz), 3.07-2.81 (br m, 6H), 2.04 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz).

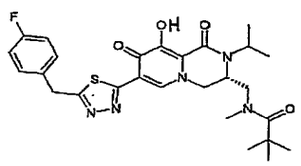
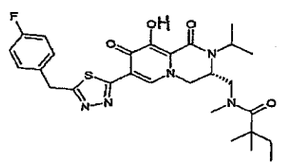
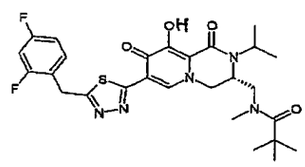
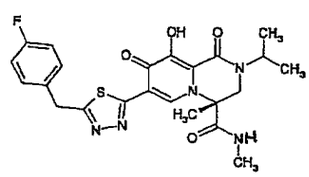
[0466]

[Table 1-50]

No.	structural formula	salt	^{1}H-NMR
178		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.87 (s, 1H), 8.55 (s, 1H), 7.44–7.37 (m, 2H), 7.22–7.14 (m, 2H), 4.48 (s, 2H), 4.15 (d, 1H, J = 13.9 Hz), 3.85 (d, 1H, J = 13.9 Hz), 2.95–2.83 (m, 1H), 2.89 (s, 6H), 1.97 (s, 3H), 0.95–0.80 (m, 2H), 0.76–0.62 (m, 2H).
179		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.90 (s, 1H), 8.65 (s, 1H), 7.45–7.38 (m, 2H), 7.23–7.15 (m, 2H), 4.70 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.14 (d, 1H, J = 13.9 Hz), 3.77 (d, 1H, J = 13.9 Hz), 3.72–3.62 (br m, 1H), 3.36–3.23 (br m, 2H), 3.20–3.09 (br m, 1H), 2.06 (s, 3H), 1.98–1.84 (br m, 1H), 1.83–1.59 (br m, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.7 Hz).
180		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.92 (s, 1H), 8.62 (s, 1H), 8.17 (t, 1H, J = 5.2 Hz), 7.44–7.37 (m, 2H), 7.23–7.15 (m, 2H), 4.71 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.10 (d, 1H, J = 13.9 Hz), 3.80 (d, 1H, J = 13.9 Hz), 3.18–2.99 (m, 2H), 1.96 (s, 3H), 1.15 (d, 3H, J = 6.7 Hz), 1.12 (d, 3H, J = 6.7 Hz), 1.01 (t, 3H, J = 7.2 Hz).
181		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.98 (br s, 1H), 8.59 (s, 1H), 7.45–7.37 (m, 2H), 7.23–7.15 (m, 2H), 4.47 (s, 2H), 4.32 (d, 1H, J = 14.4 Hz), 3.82 (d, 1H, J = 14.4 Hz), 2.90 (s, 6H), 2.03 (s, 3H), 1.45 (s, 9H).

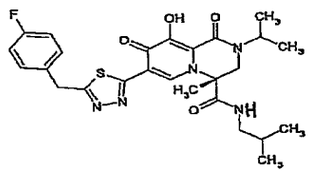
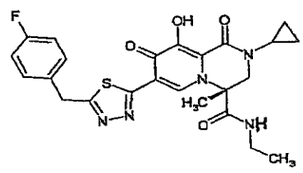
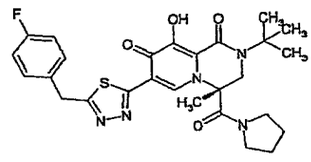
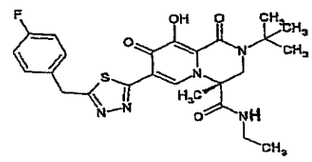
[0467]

[Table 1-51]

No.	structural formula	salt	^{1}H-NMR
182		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.91 (s, 1H), 7.44–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.55 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 4.43–4.29 (m, 2H), 4.26–4.19 (m, 1H), 3.47 (dd, 1H, J = 13.3, 4.0 Hz), 3.28 (dd, 1H, J = 13.3, 10.0 Hz), 3.12 (s, 3H), 1.35 (d, 3H, J = 6.7 Hz), 1.30 (d, 3H, J = 6.7 Hz), 1.20 (s, 9H).
183		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.92 (s, 1H), 7.44–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.55 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 4.38–4.33 (m, 2H), 4.22–4.16 (m, 1H), 3.47 (dd, 1H, J = 13.5, 3.5 Hz), 3.28 (dd, 1H, J = 13.5, 10.0 Hz), 3.12 (s, 3H), 1.65–1.57 (m, 2H), 1.35 (d, 3H, J = 6.7 Hz), 1.30 (d, 3H, J = 6.7 Hz), 1.17 (s, 3H), 1.16 (s, 3H), 0.79 (t, 3H, J = 7.5 Hz).
184		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.41 (br s, 1H), 8.90 (s, 1H), 7.58–7.50 (m, 1H), 7.32–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.56 (sep, 1H, J = 6.6 Hz), 4.49 (s, 2H), 4.41–4.29 (m, 2H), 4.27–4.18 (m, 1H), 3.48–3.44 (m, 1H), 3.29 (dd, 1H, J = 13.5, 10.0 Hz), 3.12 (s, 3H), 1.35 (d, 3H, J = 6.7 Hz), 1.30 (d, 3H, J = 6.7 Hz), 1.20 (s, 9H).
185		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.90 (br s, 1H), 8.63 (s, 1H), 8.12 (q, 1H, J = 4.4 Hz), 7.45–7.37 (m, 2H), 7.23–7.15 (m, 2H), 4.70 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.08 (d, 1H, J = 13.9 Hz), 3.80 (d, 1H, J = 13.9 Hz), 2.59 (d, 3H, J = 4.4 Hz), 1.97 (s, 3H), 1.15 (d, 3H, J = 6.7 Hz), 1.09 (d, 3H, J = 6.7 Hz).

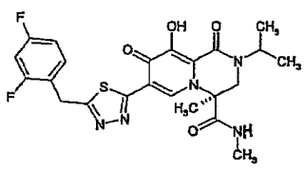
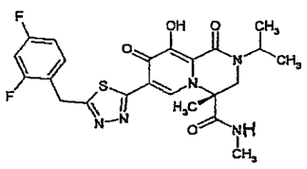
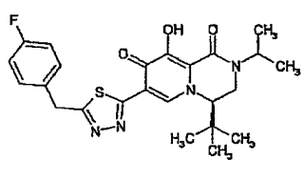
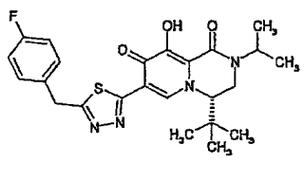
[0468]

[Table 1-52]

No.	structural formula	salt	^{1}H-NMR
186		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.93 (br s, 1H), 8.64 (s, 1H), 8.09 (t, 1H, J = 6.0 Hz), 7.43–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.69 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.14 (d, 1H, J = 13.9 Hz), 3.79 (d, 1H, J = 13.9 Hz), 3.10–3.01 (m, 1H), 2.71–2.62 (m, 1H), 1.97 (s, 3H), 1.75–1.61 (m, 1H), 1.15 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz), 0.79 (d, 6H, J = 6.7 Hz).
187		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.85 (br s, 1H), 8.62 (s, 1H), 8.19 (t, 1H, J = 5.2 Hz), 7.45–7.36 (m, 2H), 7.22–7.15 (m, 2H), 4.48 (s, 2H), 4.00 (d, 1H, J = 13.7 Hz), 3.96 (d, 1H, J = 13.7 Hz), 3.11–3.02 (m, 2H), 2.88 (sep, 1H, J = 3.9 Hz), 1.92 (s, 3H), 0.98 (t, 3H, J = 7.0 Hz), 0.96–0.89 (m, 1H), 0.85–0.69 (m, 2H), 0.65–0.56 (m, 1H).
188		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.93 (br s, 1H), 8.69 (s, 1H), 7.45–7.39 (m, 2H), 7.22–7.15 (m, 2H), 4.48 (s, 2H), 4.32 (d, 1H, J = 13.9 Hz), 3.77 (d, 1H, J = 13.9 Hz), 3.44–3.23 (br m, 4H), 2.01 (s, 3H), 1.92–1.54 (br m, 4H), 1.44 (s, 9H).
189		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.98 (br s, 1H), 8.59 (s, 1H), 8.19 (t, 1H, J = 7.0 Hz), 7.44–7.37 (m, 2H), 7.23–7.15 (m, 2H), 4.48 (s, 2H), 4.23 (d, 1H, J = 13.7 Hz), 3.83 (d, 1H, J = 13.7 Hz), 3.10 (dq, 2H, J = 7.0, 7.0 Hz), 1.94 (s, 3H), 1.45 (s, 9H), 1.02 (t, 3H, J = 7.0 Hz).

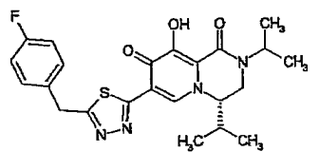
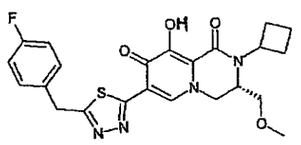
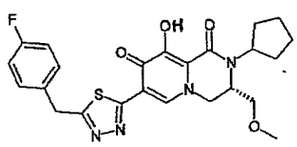
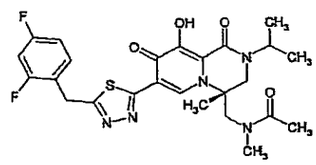
[0469]

[Table 1-53]

No.	structural formula	salt	^{1}H-NMR
190		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.90 (br s, 1H), 8.62 (s, 1H), 8.10 (q, 1H, J = 4.4 Hz), 7.53 (td, 1H, J = 8.6, 6.5 Hz), 7.28 (ddd, 1H, J = 10.2, 9.5, 2.6 Hz), 7.11 (tdd, 1H, J = 8.6, 2.6, 1.1 Hz), 4.69 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.06 (d, 1H, J = 13.9 Hz), 3.78 (d, 1H, J = 13.9 Hz), 2.58 (d, 3H, J = 4.4 Hz), 1.95 (s, 3H), 1.13 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.7 Hz).
191		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.90 (br s, 1H), 8.62 (s, 1H), 8.10 (q, 1H, J = 4.4 Hz), 7.53 (td, 1H, J = 8.6, 6.5 Hz), 7.28 (ddd, 1H, J = 10.2, 9.5, 2.6 Hz), 7.11 (tdd, 1H, J = 8.6, 2.6, 1.1 Hz), 4.69 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.06 (d, 1H, J = 13.9 Hz), 3.78 (d, 1H, J = 13.9 Hz), 2.58 (d, 3H, J = 4.4 Hz), 1.95 (s, 3H), 1.13 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.7 Hz).
192		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.88 (br s, 1H), 8.82 (s, 1H), 7.45–7.39 (m, 2H), 7.22–7.16 (m, 2H), 4.77 (sep, 1H, J = 6.9 Hz), 4.63–4.59 (m, 1H), 4.47 (s, 2H), 3.89–3.82 (m, 2H), 1.27 (d, 3H, J = 6.9 Hz), 1.19 (d, 3H, J = 6.9 Hz), 0.96 (s, 9H).
193		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.88 (br s, 1H), 8.82 (s, 1H), 7.45–7.39 (m, 2H), 7.22–7.16 (m, 2H), 4.77 (sep, 1H, J = 6.9 Hz), 4.63–4.59 (m, 1H), 4.47 (s, 2H), 3.89–3.83 (m, 2H), 1.28 (d, 3H, J = 6.9 Hz), 1.19 (d, 3H, J = 6.9 Hz), 0.96 (s, 9H).

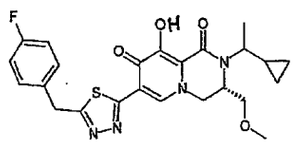
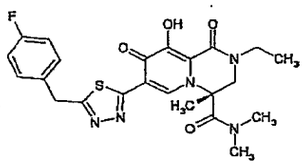
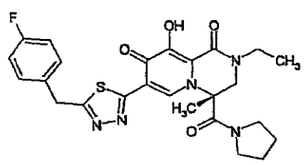
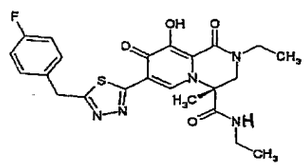
[0470]

[Table 1-54]

No.	structural formula	salt	^{1}H-NMR
194		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.76 (br s, 1H), 8.90 (s, 1H), 7.45-7.39 (m, 2H), 7.22-7.16 (m, 2H), 4.79-4.79 (sep, 1H, J = 6.7 Hz), 4.50-4.43 (m, 1H), 4.47 (s, 2H), 3.86-3.78 (m, 2H), 2.03-1.92 (m, 1H), 1.20 (d, 3H, J = 6.7 Hz), 1.18 (d, 3H, J = 6.7 Hz), 1.04 (d, 3H, J = 6.7 Hz), 0.69 (d, 3H, J = 6.7 Hz).
195		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.49 (br s, 1H), 8.85 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.68 (dd, 1H, J = 13.5, 1.3 Hz), 4.61-4.49 (m, 1H), 4.47 (s, 2H), 4.41 (dd, 1H, J = 13.5, 4.0 Hz), 4.31-4.25 (m, 1H), 3.43 (dd, 1H, J = 10.6, 5.0 Hz), 3.39 (dd, 1H, J = 10.6, 6.8 Hz), 3.21 (s, 3H), 2.38-2.11 (m, 4H), 1.77-1.64 (m, 2H).
196		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.49 (br s, 1H), 8.85 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.15 (m, 2H), 4.65 (dd, 1H, J = 13.7, 1.5 Hz), 4.47 (s, 2H), 4.44-4.34 (m, 2H), 4.20-4.13 (m, 1H), 3.47 (dd, 1H, J = 10.4, 4.6 Hz), 3.41 (dd, 1H, J = 10.4, 7.3 Hz), 3.21 (s, 3H), 1.95-1.72 (m, 6H), 1.63-1.49 (m, 2H).
197		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.29 (br s, 1H), 8.52 (s, 1H), 7.60-7.50 (m, 1H), 7.36-7.25 (m, 1H), 7.17-7.08 (m, 1H), 4.86-4.73 (m, 1H), 4.49 (s, 2H), 3.91-3.64 (m, 4H), 2.82 (s, 3H), 1.81 (s, 3H), 1.71 (s, 3H), 1.23 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 7.0 Hz).

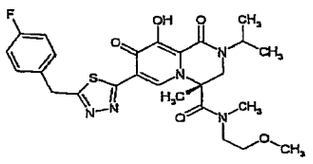
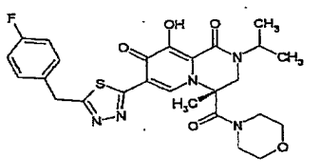
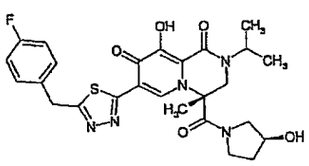
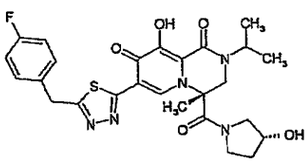
[0471]

[Table 1-55]

No.	structural formula	salt	^{1}H-NMR
198		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.88 (s, 1H), 7.45–7.37 (m, 2H), 7.23–7.15 (m, 2H), 4.70 (d, 1H, J = 13.0 Hz), 4.47 (s, 2H), 4.39–4.27 (m, 2H), 3.73–3.61 (m, 2H), 3.49–3.41 (m, 1H), 3.22 (s, 3H), 1.34 (d, 3H, J = 6.7 Hz), 1.26–1.13 (m, 1H), 0.69–0.60 (m, 1H), 0.54–0.45 (m, 1H), 0.42–0.27 (m, 2H).
199		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.87 (s, 1H), 8.56 (s, 1H), 7.45–7.37 (m, 2H), 7.23–7.15 (m, 2H), 4.48 (s, 2H), 4.21 (d, 1H, J = 13.9 Hz), 3.98 (d, 1H, J = 13.9 Hz), 3.53 (q, 2H, J = 7.0 Hz), 2.50 (s, 6H), 2.01 (s, 3H), 1.11 (t, 3H, J = 7.0 Hz).
200		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.81 (br s, 1H), 8.67 (s, 1H), 7.45–7.39 (m, 2H), 7.22–7.15 (m, 2H), 4.48 (s, 2H), 4.19 (d, 1H, J = 13.9 Hz), 3.96 (d, 1H, J = 13.9 Hz), 3.59–3.25 (br m, 3H), 3.53 (dq, 1H, J = 14.0, 7.0 Hz), 3.49 (dq, 1H, J = 14.0, 7.0 Hz), 3.12–2.96 (br m, 1H), 2.01 (s, 3H), 1.96–1.48 (m, 4H), 1.09 (t, 3H, J = 7.0 Hz).
201		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.81 (br s, 1H), 8.62 (s, 1H), 8.26 (t, 1H, J = 5.6 Hz), 7.44–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.48 (s, 2H), 4.13 (d, 1H, J = 13.9 Hz), 4.01 (d, 1H, J = 13.9 Hz), 3.62 (dq, 1H, J = 14.2, 7.1 Hz), 3.36 (dq, 1H, J = 14.2, 7.1 Hz), 3.14–3.04 (m, 2H), 1.93 (s, 3H), 1.11 (t, 3H, J = 7.1 Hz), 1.00 (t, 3H, J = 7.1 Hz).

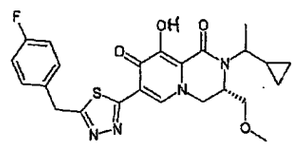
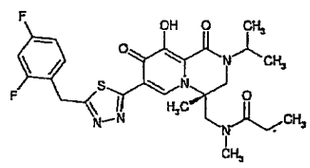
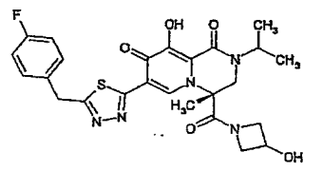
[0472]

[Table 1-56]

No.	structural formula	salt	^{1}H-NMR
202		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.00 (br s, 1H), 8.57 (s, 1H), 7.45-7.37 (m, 2H), 7.22-7.15 (m, 2H), 4.72 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.18 (d, 1H, J = 14.4 Hz), 3.81 (d, 1H, J = 14.4 Hz), 3.64 (br s, 3H), 3.42 (t, 2H, J = 5.3 Hz), 3.20 (s, 3H), 3.05-2.92 (br m, 2H), 2.02 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.13 (d, 3H, J = 6.7 Hz).
203		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.06 (br s, 1H), 8.52 (s, 1H), 7.46-7.38 (m, 2H), 7.23-7.15 (m, 2H), 4.75 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.05 (d, 1H, J = 14.4 Hz), 3.84 (d, 1H, J = 14.4 Hz), 3.62-3.48 (br m, 8H), 1.98 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
204		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.95 (br s, 1H), 8.68-8.61 (m, 1H), 7.45-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.69 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.23-4.15 (br m, 1H), 4.11 (d, 1H, J = 13.9 Hz), 3.76 (d, 1H, J = 13.9 Hz), 3.69-3.59 (br m, 1H), 3.46-3.36 (br m, 2H), 3.30-2.88 (br m, 1H), 2.09-2.00 (m, 3H), 2.02-1.55 (br m, 2H), 1.21-1.06 (m, 6H).
205		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.91 (br s, 1H), 8.71-8.61 (m, 1H), 7.46-7.37 (m, 2H), 7.24-7.14 (m, 2H), 4.69 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.33-4.13 (br m, 2H), 4.08 (d, 1H, J = 13.9 Hz), 3.77 (d, 1H, J = 13.9 Hz), 3.51-3.15 (br m, 3H), 2.14-2.01 (m, 3H), 1.89-1.61 (br m, 2H), 1.21-1.02 (m, 6H).

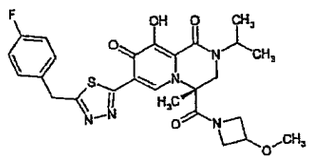
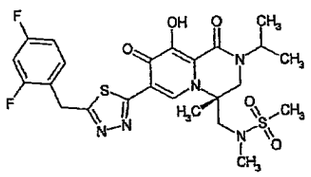
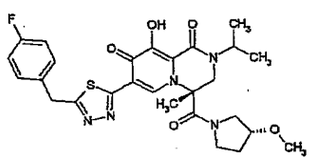
[0473]

[Table 1-57]

No.	structural formula	salt	^{1}H-NMR
206		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.87 (s, 1H), 7.44–7.38 (m, 2H), 7.23–7.15 (m, 2H), 4.72 (d, 1H, J = 12.3 Hz), 4.47 (s, 2H), 4.43–4.33 (m, 2H), 3.67–3.58 (m, 1H), 3.57–3.51 (m, 1H), 3.47–3.40 (m, 1H), 3.22 (s, 3H), 1.34 (d, 3H, J = 6.7 Hz), 1.31–1.21 (m, 1H), 0.68–0.59 (m, 1H), 0.54–0.46 (m, 1H), 0.44–0.36 (m, 1H), 0.32–0.24 (m, 1H).
207		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.31 (br s, 1H), 8.48 (s, 1H), 7.59–7.49 (m, 1H), 7.38–7.22 (m, 1H), 7.20–7.05 (m, 1H), 4.87–4.73 (m, 1H), 4.48 (s, 2H), 4.02–3.86 (m, 1H), 3.80 (d, 1H, J = 13.7 Hz), 3.71 (d, 1H, J = 13.7 Hz), 3.47–3.32 (m, 1H), 2.85 (s, 3H), 2.17–2.04 (m, 2H), 1.71 (s, 3H), 1.23 (d, 3H, J = 7.0 Hz), 1.17 (d, 3H, J = 7.0 Hz), 0.65 (t, 3H, J = 7.4 Hz).
208		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.93 (br s, 1H), 8.72 (s, 1H), 7.45–7.38 (m, 2H), 7.23–7.15 (m, 2H), 4.69 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.44–4.27 (br m, 2H), 4.11–3.82 (br m, 2H), 4.02 (d, 1H, J = 13.9 Hz), 3.72 (d, 1H, J = 13.9 Hz), 3.64–3.40 (br m, 1H), 1.99 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.12 (d, 3H, J = 6.7 Hz).

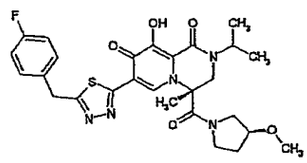
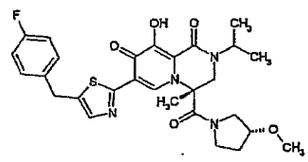
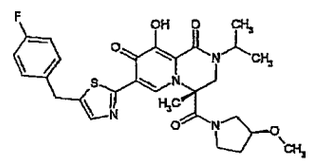
[0474]

[Table 1-58]

No.	structural formula	salt	^{1}H-NMR
209		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.89 (br s, 1H), 8.71 (s, 1H), 7.45–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.70 (sep, 1H, J = 6.8 Hz), 4.48 (s, 2H), 4.22–3.90 (br m, 4H), 4.00 (d, 1H, J = 13.9 Hz), 3.74–3.57 (br m, 1H), 3.74 (d, 1H, J = 13.9 Hz), 3.14 (s, 3H), 2.00 (s, 3H), 1.19–1.09 (m, 6H).
210		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.30 (s, 1H), 8.60 (s, 1H), 7.56–7.50 (m, 1H), 7.35–7.25 (m, 1H), 7.13–7.08 (m, 1H), 4.80–4.74 (m, 1H), 4.47 (s, 2H), 3.75 (s, 2H), 3.48–3.30 (m, 2H), 2.84 (s, 3H), 2.57 (s, 3H), 1.74 (s, 3H), 1.24 (d, 3H, J=6.7 Hz), 1.15 (d, 3H, J=6.7 Hz).
211		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.91 (s, 0.5H), 12.86 (s, 0.5H), 8.68 (s, 0.5H), 8.60 (s, 0.5H), 7.42–7.38 (m, 2H), 7.20–7.15 (m, 2H), 4.72–4.65 (m, 1H), 4.47 (s, 2H), 4.16 (d, 0.5H, J = 13.7Hz), 4.08 (d, 0.5H, J = 13.7 Hz), 4.00–3.98 (m, 0.5H), 3.86–3.84 (m, 0.5H) 3.81–3.74 (m, 2H), 3.51–3.33 (m, 3H), 3.17 (s, 3H), 2.54–2.49 (m, 2H), 2.07 (s, 3H), 1.15 (d, 3H, J=6.7 Hz), 1.05 (d, 3H, J=6.7 Hz).

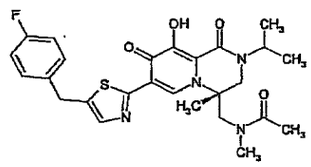
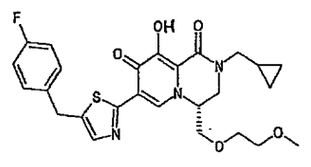
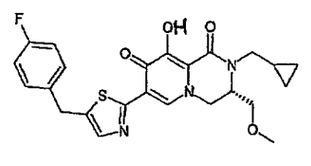
[0475]

[Table 1-59]

No.	structural formula	salt	^{1}H-NMR
212		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.94 (s, 1H), 8.66 (s, 0.5H), 8.62 (s, 0.5H), 7.42–7.38 (m, 2H), 7.20–7.15 (m, 2H), 4.70–4.65 (m, 1H), 4.47 (s, 2H), 4.11–4.06 (m, 1H), 3.93–3.90 (m, 1H), 3.87–3.84 (m, 1H), 3.81–3.75 (m, 1H) 3.69–3.65 (m, 1H), 3.62–3.45 (m, 1H), 3.17 (s, 1.5H), 3.15 (s, 1.5H), 3.10–3.06 (m, 1H), 2.07 (s, 1.5H), 2.05 (s, 1.5H), 1.99–1.96 (m, 1H), 1.79–1.76 (m, 1H), 1.16 (d, 3H, J=6.7 Hz), 1.06 (d, 3H, J=6.7 Hz).
213		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (br s, 1H), 8.55 (s, 0.5H), 8.48 (s, 0.5H), 7.67 (s, 1H), 7.34–7.29 (m, 2H), 7.17–7.11 (m, 2H), 4.71–4.65 (m, 1H), 4.25–4.04 (m, 1H), 4.20 (s, 2H), 3.98–3.86 (m, 0.5H), 3.85–3.84 (m, 0.5H), 3.78–3.68 (m, 2H), 3.50–3.25 (m, 2H), 3.17 (s, 1.5H), 3.15 (s, 1.5H), 2.54–2.49 (m, 1H), 2.02 (s, 3H), 1.91–1.85 (m, 1H), 1.78–1.71 (m, 1H), 1.15 (d, 3H, J = 6.7 Hz), 1.05 (d, 3H, J=6.7 Hz).
214		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.84 (br s, 1H), 8.54 (s, 0.5H), 8.50 (s, 0.5H), 7.68 (s, 1H), 7.34–7.31 (m, 2H), 7.17–7.11 (m, 2H), 4.71–4.65 (m, 1H), 4.20 (s, 2H), 4.07 (dd, 1H, J=13.9, 5.3 Hz), 3.90–3.85 (m, 1H), 3.75 (dd, 1H, J=13.9, 7.4 Hz), 3.59–3.36 (m, 3H), 3.15 (s, 3H), 2.54–2.49 (m, 1H), 2.02 (s, 1.5H), 1.99 (s, 1.5H), 1.99–1.97 (m, 1H), 1.78–1.71 (m, 1H), 1.16 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J=6.7 Hz).

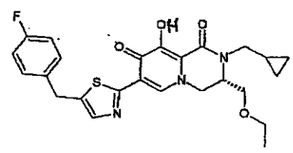
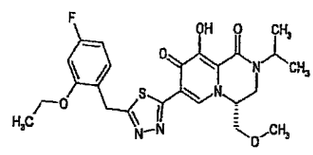
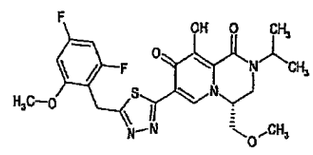
[0476]

[Table 1-60]

No.	structural formula	salt	^{1}H-NMR
215		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.20 (br s, 1H), 8.44 (s, 1H), 7.67 (s, 1H), 7.35-7.31 (m, 2H), 7.16-7.11 (m, 2H), 4.81-4.74 (m, 1H), 4.19 (s, 2H), 3.79-3.65 (m, 3H), 3.57 (d, 1H, J=14.4 Hz), 2.74 (s, 3H), 1.81 (s, 3H), 1.66 (s, 3H), 1.21 (d, 3H, J=6.7 Hz), 1.15 (d, 3H, J=6.7 Hz).
216		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.60 (br s, 1H), 8.63 (s, 1H), 7.66 (s, 1H), 7.35-7.30 (m, 2H), 7.17-7.11 (m, 2H), 4.89-4.85 (m, 1H), 4.19 (s, 2H), 4.08 (dd, 1H, J=13.7, 4.2 Hz), 3.81 (d, 1H, J=13.7 Hz), 3.57 (dd, 1H, J=10.5, 5.7 Hz), 3.66 (dd, 1H, J=10.5, 7.9 Hz), 3.56-3.39 (m, 3H), 3.33-3.27 (m, 3H), 3.10 (s, 3H), 1.10-1.04 (m, 1H), 0.55-0.46 (m, 2H), 0.36-0.26 (m, 2H).
217		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.30 (br s, 1H), 8.65 (s, 1H), 7.66 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.60 (d, 1H, J=13.2 Hz), 4.42 (dd, 1H, J=13.2, 3.9 Hz), 4.24-4.19 (m, 1H), 4.19 (s, 2H), 3.67 (dd, 1H, J=14.2, 7.0 Hz), 3.55 (dd, 1H, J=10.3, 4.8 Hz), 3.47 (dd, 1H, J=10.3, 7.0 Hz), 3.20 (s, 3H), 3.19 (dd, 1H, J=14.2, 7.4 Hz), 1.18-1.12 (m, 1H), 0.55-0.46 (m, 2H), 0.41-0.37 (m, 1H), 0.31-0.28 (m, 1H).

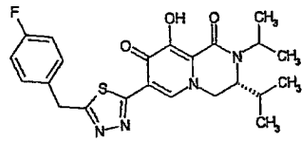
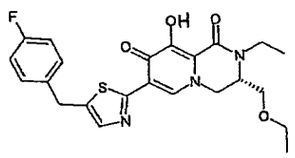
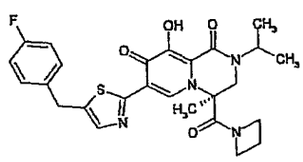
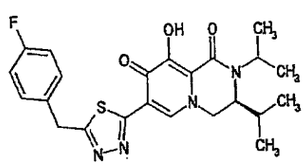
[0477]

[Table 1-61]

No.	structural formula	salt	^{1}H-NMR
218		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.30 (br s, 1H), 8.65 (s, 1H), 7.66 (s, 1H), 7.34–7.31 (m, 2H), 7.16–7.11 (m, 2H), 4.61 (d, 1H, J=13.5 Hz), 4.42 (dd, 1H, J=13.5, 4.2 Hz), 4.24–4.19 (m, 1H), 4.19 (s, 2H), 3.67 (dd, 1H, J=14.0, 7.1 Hz), 3.60 (dd, 1H, J=10.3, 4.2 Hz), 3.52 (dd, 1H, J=10.3, 6.4 Hz), 3.42–3.30 (m, 2H), 3.20 (dd, 1H, J=14.0, 7.0 Hz), 1.16–1.11 (m, 1H), 0.95 (t, 3H, J=7.0 Hz), 0.56–0.46 (m, 2H), 0.41–0.37 (m, 1H), 0.31–0.27 (m, 1H).
219		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.79 (br s, 1H), 8.78 (s, 1H), 7.35 (dd, 1H, J = 8.4, 7.0 Hz), 6.93 (dd, 1H, J = 11.4, 2.6 Hz), 6.74 (td, 1H, J = 8.4, 2.6 Hz), 4.97–4.93 (m, 1H), 4.79–4.72, (m, 1H), 4.33 (s, 2H), 4.06 (q, 2H, J=7.0 Hz), 3.79–3.65 (m, 2H), 3.61 (dd, 1H, J=10.3, 5.7 Hz), 3.55 (dd, 1H, J=10.3, 7.7 Hz), 3.23 (s, 3H), 1.31 (t, 3H, J=7.0 Hz), 1.15 (d, 3H, J=2.3 Hz), 1.14 (d, 3H, J=2.3 Hz).
220		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (s, 1H), 8.76 (s, 1H), 6.93–6.87 (m, 2H), 4.97–4.93 (m, 1H), 4.79–4.72 (m, 1H), 4.33 (s, 2H), 3.85 (s, 3H), 3.84–3.72 (m, 2H), 3.61 (dd, 1H, J=10.3, 5.7 Hz), 3.55 (dd, 1H, J=10.3, 7.8 Hz), 3.23 (s, 3H), 1.15 (d, 3H, J=2.3 Hz), 1.14 (d, 3H, J=2.3 Hz).

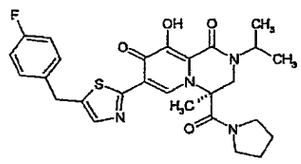
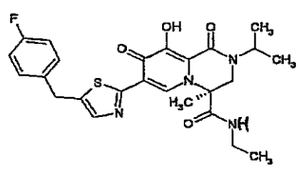
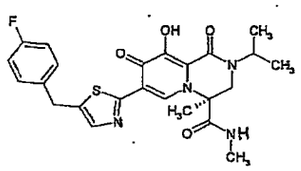
[0478]

[Table 1-62]

No.	structural formula	salt	^{1}H-NMR
221		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.50 (br s, 1H), 9.02 (s, 1H), 7.43–7.39 (m, 2H), 7.21–7.16 (m, 2H), 4.76 (d, 1H, J=13.3 Hz), 4.47 (s, 2H), 4.30 (dd, 1H, J=13.3, 4.6 Hz), 4.21–4.14 (m, 1H), 3.83 (br t, 1H, J=4.6 Hz), 2.04–1.99 (m, 1H), 1.39 (d, 3H, J=6.9 Hz), 1.35 (d, 3H, J=6.9 Hz), 1.05 (d, 3H, J=6.9Hz), 0.64 (d, 3H, J=6.9 Hz).
222		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.30 (br s, 1H), 8.65 (s, 1H), 7.67 (s, 1H), 7.35–7.31 (m, 2H), 7.18–7.13 (m, 2H), 4.59, (br d, 1H, J=13.3 Hz), 4.41 (dd, 1H, J=13.3, 4.1 Hz), 4.20 (s, 2H), 4.12–4.09 (m, 1H), 3.89–3.84 (m, 1H), 3.58–3.50 (m, 2H), 3.41–3.34 (m, 2H), 3.29–3.24 (m, 1H), 1.20 (t, 3H, J=7.2 Hz), 0.97 (t, 3H, J=7.0Hz).
223		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (m, 1H), 8.59 (s, 1H), 7.69 (s, 1H), 7.34–7.30 (m, 2H), 7.17–7.11 (m, 2H), 4.72–4.65 (m, 1H), 4.20 (s, 2H), 4.20–4.13 (m, 1H), 4.00 (d, 1H, J=13.5 Hz), 3.86–3.80 (m, 2H), 3.75–3.66 (m, 2H), 2.12–2.03 (m, 2H), 1.93 (s, 3H), 1.14 (d, 3H, J=6.7 Hz), 1.12 (d, 3H, J=6.7 Hz).
224		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.55 (br s, 1H), 9.02 (s, 1H), 7.43–7.39 (m, 2H), 7.21–7.16 (m, 2H), 4.76 (d, 1H, J=13.3 Hz), 4.47 (s, 2H), 4.30 (dd, 1H, J=13.3, 4.6 Hz), 4.21–4.14 (m, 1H), 3.83 (br t, 1H, J=4.6 Hz), 2.04–1.99 (m, 1H), 1.39 (d, 3H, J = 6.9 Hz), 1.35 (d, 3H, J=6.9 Hz), 1.05 (d, 3H, J=6.9 Hz), 0.64 (d, 3H, J=6.9 Hz).

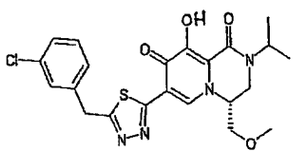
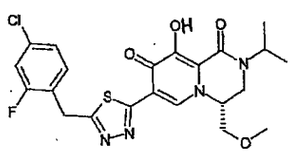
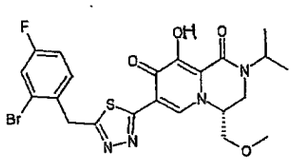
[0479]

[Table 1-63]

No.	structural formula	salt	^{1}H-NMR
225		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.78 (s, 1H), 8.52 (s, 1H), 7.67 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.12 (m, 2H), 4.72-4.66 (m, 1H), 4.19 (s, 2H), 4.11 (d, 1H, J=13.9 Hz), 3.74 (d, 1H, J=13.9 Hz), 3.41-3.25 (m, 1H), 3.13-3.06 (m, 1H), 3.81-3.74 (m, 2H), 2.00 (s, 3H), 1.92-1.84 (m, 1H), 1.75-1.61 (m, 3H), 1.15 (d, 3H, J=6.7 Hz), 1.07 (d, 3H, J=6.7 Hz).
226		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.81 (br s, 1H), 8.51 (s, 1H), 8.20 (br t, 1H, J=5.5 Hz), 7.67 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.73-4.66 (m, 1H), 4.20 (s, 2H), 4.11 (d, 1H, J=13.7 Hz), 3.77 (d, 1H, J=13.7 Hz), 3.13-2.99 (m, 2H), 1.92 (s, 3H), 1.14 (d, 3H, J=6.7 Hz), 1.10 (d, 3H, J=6.7 Hz), 0.99 (t, 3H, J=7.2 Hz).
227		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (br s, 1H), 8.54 (s, 1H), 8.22 (d, 1H, J=4.4 Hz), 7.69 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.12 (m, 2H), 4.73-4.66 (m, 1H), 4.20 (s, 2H), 4.13 (d, 1H, J=13.7 Hz), 3.78 (d, 1H, J=13.7 Hz), 2.57 (d, 3H, J=4.4 Hz), 1.93 (s, 3H), 1.13 (d, 3H, J=7.0 Hz), 1.08 (d, 3H, J=7.0 Hz).

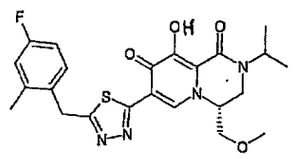
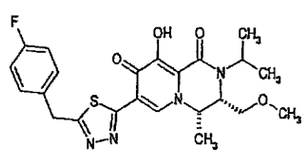
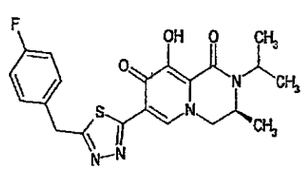
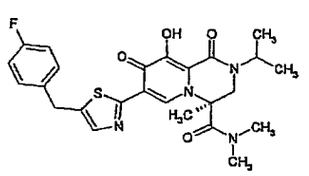
[0480]

[Table 1-64]

No.	structural formula	salt	^{1}H-NMR
228		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.85 (br s, 1H), 8.81 (s, 1H), 7.48-7.46 (m, 1H), 7.42-7.33 (m, 3H), 4.98-4.96 (m, 1H), 4.80-4.73 (m, 1H), 4.50 (s, 2H), 3.84 (dd, 1H, J=13.8, 4.1 Hz), 3.75 (br d, 1H, J=13.8 Hz), 3.63 (dd, 1H, J=10.4, 5.7 Hz), 3.57 (dd, 1H, J=10.4, 7.5 Hz), 3.25 (s, 3H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz).
229		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.83 (br s, 1H), 8.80 (s, 1H), 7.51 (t, 1H, J=8.3 Hz), 7.48 (dd, 1H, J=8.3, 2.0 Hz), 7.32 (dd, 1H, J=8.3, 2.0 Hz), 5.00-4.95 (m, 1H), 4.80-4.74 (m, 1H), 4.50 (s, 2H), 3.84 (dd, 1H, J=13.7, 4.0 Hz), 3.75 (dd, 1H, J=13.7, 1.6 Hz), 3.62 (dd, 1H, J=10.3, 5.8 Hz), 3.57 (dd, 1H, J=10.3, 7.7 Hz), 3.25 (s, 3H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz).
230		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.83 (br s, 1H), 8.79 (s, 1H), 7.66 (dd, 1H, J=8.7, 2.6 Hz), 7.61 (dd, 1H, J=8.7, 6.0 Hz), 7.32 (td, 1H, J=8.7, 2.6 Hz), 4.99-4.95 (m, 1H), 4.80-4.74 (m, 1H), 4.57 (s, 2H), 3.84 (dd, 1H, J=13.7, 4.0 Hz), 3.75 (dd, 1H, J=13.7, 1.6 Hz), 3.62 (dd, 1H, J=10.3, 5.8 Hz), 3.57 (dd, 1H, J=10.3, 7.7 Hz), 3.25 (s, 3H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz).

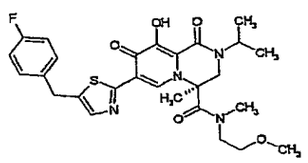
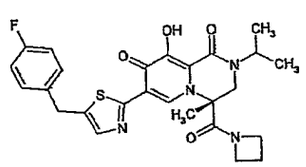
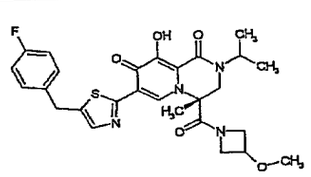
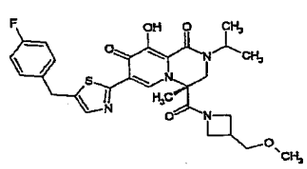
[0481]

[Table 1-65]

No.	structural formula	salt	^{1}H-NMR
231		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (br s, 1H), 8.79 (s, 1H), 7.37 (dd, 1H, J=8.5, 6.1 Hz), 7.10-7.01 (m, 2H), 4.99-4.95 (m, 1H), 4.80-4.74 (m, 1H), 4.45 (s, 2H), 3.84 (dd, 1H, J=13.7, 4.1 Hz), 3.75 (br d, 1H, J=13.7 Hz), 3.62 (dd, 1H, J=10.4, 5.7 Hz), 3.57 (dd, 1H, J=10.4, 7.6 Hz), 3.25 (s, 3H), 2.29 (s, 3H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz).
232		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.75 (br s, 1H), 8.56 (s, 1H), 7.42-7.38 (m, 2H), 7.20-7.16 (m, 2H), 4.66-4.64 (m, 1H), 4.47 (s, 2H), 4.45-4.40 (m, 1H), 4.08-4.05 (m, 1H), 3.56 (dd, 1H, J=11.3, 3.2 Hz), 3.50 (dd, 1H, J=11.3, 4.2 Hz), 3.11 (s, 3H), 1.75 (d, 3H, J=6.5 Hz), 1.33 (d, 3H, J=6.0 Hz), 1.32 (d, 3H, J=6.0 Hz).
233		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.54 (br s, 1H), 8.85 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.62-4.53 (m, 1H), 4.51-4.44 (m, 3H), 4.32 (dd, 1H, J = 13.1, 3.4 Hz), 4.26-4.18 (m, 1H), 1.27 (d, 3H, J = 6.7 Hz), 1.26 (d, 3H, J = 6.7 Hz), 1.21 (d, 3H, J = 6.5 Hz).
234		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.85 (s, 1H), 8.43 (s, 1H), 7.69 (s, 1H), 7.37-7.29 (m, 2H), 7.19-7.11 (m, 2H), 4.73 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.12 (d, 1H, J = 14.1 Hz), 3.79 (d, 1H, J = 14.1 Hz), 2.93 (s, 6H), 1.98 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz).

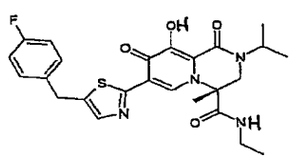
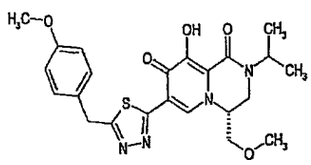
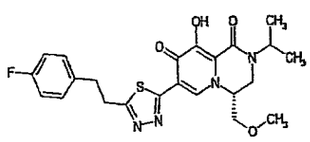
[0482]

[Table 1-66]

No.	structural formula	salt	^{1}H-NMR
235		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.89 (br s, 1H), 8.46 (s, 1H), 7.69 (s, 1H), 7.34–7.31 (m, 2H), 7.16–7.12 (m, 2H), 4.74–4.68 (m, 1H), 4.20 (s, 2H), 4.15 (d, 1H, J = 14.2 Hz), 3.78 (d, 1H, J = 14.2 Hz), 3.60–3.53 (m, 1H), 3.40 (br t, 2H, J = 5.2 Hz), 3.36–3.28 (m, 1H), 3.18 (s, 3H), 2.95 (br s, 3H), 1.97 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.12 (d, 3H, J = 6.7 Hz).
236		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.80 (m, 1H), 8.59 (s, 1H), 7.69 (s, 1H), 7.34–7.30 (m, 2H), 7.17–7.11 (m, 2H), 4.72–4.65 (m, 1H), 4.20 (s, 2H), 4.20–4.13 (m, 1H), 4.00 (d, 1H, J=13.5 Hz), 3.86–3.80 (m, 2H), 3.75–3.66 (m, 2H), 2.12–2.03 (m, 2H), 1.93 (s, 3H), 1.14 (d, 3H, J=6.7 Hz), 1.12 (d, 3H, J=6.7 Hz).
237		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.77 (br s, 1H), 8.55 (s, 1H), 7.69 (s, 1H), 7.34–7.30 (m, 2H), 7.17–7.11 (m, 2H), 4.72–4.66 (m, 1H), 4.20 (s, 2H), 4.17–3.96 (m, 4H), 3.73–3.53 (m, 3H), 3.12 (s, 3H), 2.95 (s, 3H), 1.18–1.07 (m, 6H).
238		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.80 (br s, 1H), 8.58–8.53 (m, 1H), 7.69–7.68 (m, 1H), 7.34–7.30 (m, 2H), 7.16–7.12 (m, 2H), 4.72–4.66 (m, 2H), 4.20 (s, 2H), 3.99–3.84 (m, 2H), 3.78–3.67 (m, 1H), 3.60–3.47 (m, 2H), 3.36–3.33 (m, 2H), 3.27–3.25 (m, 1H), 3.28–3.16 (m, 3H), 1.93 (s, 3H), 1.15–1.10 (m, 6H).

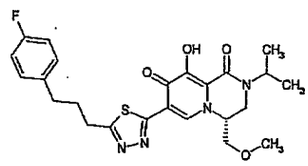
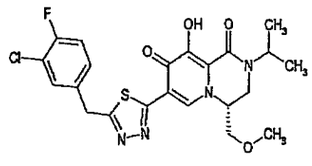
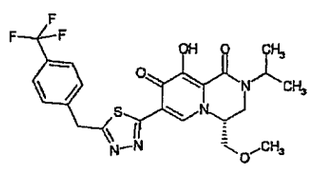
[0483]

[Table 1-67]

No.	structural formula	salt	^{1}H-NMR
239		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.81 (br s, 1H), 8.51 (s, 1H), 8.20 (br t, 1H, J=5.5 Hz), 7.67 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.73-4.66 (m, 1H), 4.20 (s, 2H), 4.11 (d, 1H, J=13.7 Hz), 3.77 (d, 1H, J=13.7 Hz), 3.13-2.99 (m, 2H), 1.92 (s, 3H), 1.14 (d, 3H, J=6.7 Hz), 1.10 (d, 3H, J=6.7 Hz), 0.99 (t, 3H, J=7.2 Hz).
240		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.80 (br s, 1H), 8.80 (s, 1H), 7.29 (d, 2H, J=8.9 Hz), 6.92 (d, 2H, J=8.9 Hz), 4.99-4.94 (m, 1H), 4.80-4.73 (m, 1H), 4.39 (s, 2H), 3.84 (dd, 1H, J=13.7, 4.0 Hz), 3.75 (d, 1H, J=13.7 Hz), 3.74 (s, 3H), 3.62 (dd, 1H, J=10.3, 5.8 Hz), 3.57 (dd, 1H, J=10.3, 7.7 Hz), 3.25 (s, 3H), 1.17 (d, 3H, J=2.4 Hz), 1.15 (d, 3H, J=2.4 Hz).
241		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.80 (br s, 1H), 8.80 (s, 1H), 7.32 (dd, 2H, J=8.5, 5.6 Hz), 7.11 (t, 2H, J=8.5 Hz), 4.98-4.94 (m, 1H), 4.81-4.74 (m, 1H), 3.84 (dd, 1H, J=13.9, 3.8 Hz), 3.76 (d, 1H, J=13.9 Hz), 3.63 (dd, 1H, J=10.3, 5.8 Hz), 3.57 (dd, 1H, J=10.3, 7.5 Hz), 3.41 (t, 2H, J=7.7 Hz), 3.26 (s, 3H), 3.09 (t, 2H, J=7.7 Hz), 1.17 (d, 3H, J=1.6 Hz), 1.15 (d, 3H, J=1.6 Hz).

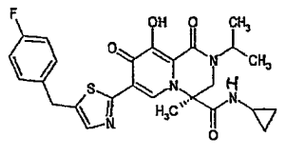
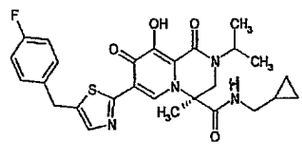
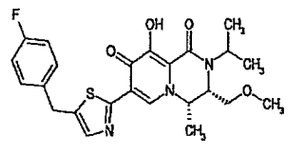
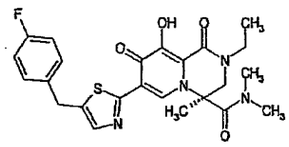
[0484]

[Table 1-68]

No.	structural formula	salt	^{1}H-NMR
242		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.81 (br s, 1H), 8.81 (s, 1H), 7.28 (dd, 2H, J=8.5, 5.6 Hz), 7.11 (t, 2H, J=8.5 Hz), 4.98-4.94 (m, 1H), 4.81-4.74 (m, 1H), 3.85 (dd, 1H, J=13.9, 4.0 Hz), 3.76 (dd, 1H, J=13.9, 1.4 Hz), 3.63 (dd, 1H, J=10.3, 5.8 Hz), 3.58 (dd, 1H, J=10.3, 7.7 Hz), 3.26 (s, 3H), 3.10 (t, 2H, J=7.7 Hz), 2.68 (t, 2H, J=7.7 Hz), 2.09-2.01 (m, 2H), 1.18 (d, 3H, J=2.0 Hz), 1.16 (d, 3H, J=2.0 Hz).
243		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.81 (s, 1H), 7.65-7.63 (m, 1H), 7.41-7.39 (m, 2H), 5.00-4.95 (m, 1H), 4.80-4.74 (m, 1H), 4.50 (s, 2H), 3.84 (dd, 1H, J=13.7, 4.0 Hz), 3.76 (dd, 1H, J=13.7, 1.6 Hz), 3.63 (dd, 1H, J=10.1, 5.6 Hz), 3.57 (dd, 1H, J=10.1, 7.7 Hz), 3.25 (s, 3H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz).
244		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.81 (s, 1H), 7.73 (d, 2H, J=8.1 Hz), 7.60 (d, 2H, J=8.1 Hz), 4.99-4.94 (m, 1H), 4.80-4.73 (m, 1H), 4.61 (s, 2H), 3.84 (dd, 1H, J=13.7, 4.0 Hz), 3.76 (dd, 1H, J=13.7, 1.6 Hz), 3.63 (dd, 1H, J=10.1, 5.6 Hz), 3.57 (dd, 1H, J=10.1, 7.7 Hz), 3.25 (s, 3H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz).

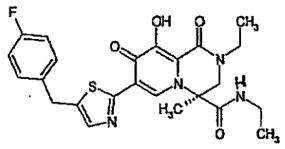
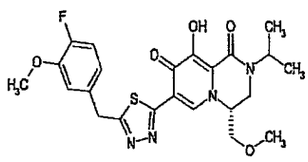
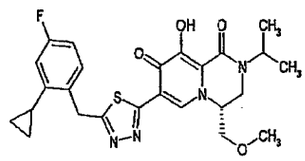
[0485]

[Table 1-69]

No.	structural formula	salt	^{1}H-NMR
245		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.79 (br s, 1H), 8.48 (s, 1H), 8.34-8.33 (m, 1H), 7.67 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.12 (m, 2H), 4.73-4.67 (m, 1H), 4.20 (s, 2H), 4.06 (d, 1H, J=13.7 Hz), 3.78 (d, 1H, J=13.7 Hz), 3.61-3.44 (m, 1H), 1.90 (s, 3H), 1.13 (d, 3H, J=6.7 Hz), 1.09 (d, 3H, J=6.7 Hz), 0.62 (d, 2H, J=7.4 Hz), 0.46-0.41 (m, 2H).
246		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.82 (br s, 1H), 8.51 (s, 1H), 8.28 (t, 1H, J=5.5 Hz), 7.67 (s, 1H), 7.33-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.73-4.66 (m, 1H), 4.20 (s, 2H), 4.15 (d, 1H, J=13.9 Hz), 3.78 (d, 1H, J=13.9 Hz), 2.98-2.84 (m, 2H), 1.93 (s, 3H), 1.14 (d, 3H, J=7.2 Hz), 1.12 (d, 3H, J=7.2 Hz), 0.89-0.85 (m, 1H), 0.40-0.37 (m, 2H), 0.14-0.10 (m, 2H).
247		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.70 (br s, 1H), 8.51 (s, 1H), 7.71 (s, 1H), 7.34-7.30 (m, 2H), 7.18-7.12 (m, 2H), 4.64-4.62 (m, 1H), 4.45-4.49 (m, 1H), 4.21 (s, 2H), 4.06-4.02 (m, 1H), 3.53 (dd, 1H, J=11.1, 3.4 Hz), 3.48 (dd, 1H, J=11.1, 4.2 Hz), 3.11 (s, 3H), 1.72 (d, 3H, J=6.5 Hz), 1.33 (d, 3H, J=5.6 Hz), 1.31 (d, 3H, J=5.6 Hz).
248		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.77 (br s, 1H), 8.44 (s, 1H), 7.68 (s, 1H), 7.37-7.29 (m, 2H), 7.16-7.11 (m, 2H), 4.20 (s, 2H), 4.19 (d, 1H, J = 14.1 Hz), 3.93 (d, 1H, J = 14.1 Hz), 3.56-3.44 (m, 2H), 2.90 (s, 6H), 1.94 (s, 3H), 1.10 (s, 3H, J=7.2 Hz).

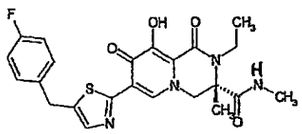
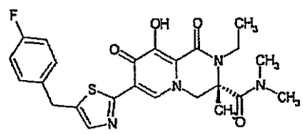
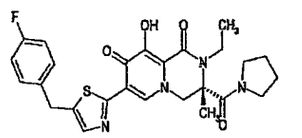
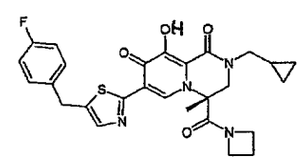
[0486]

[Table 1-70]

No.	structural formula	salt	^{1}H-NMR
249		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.68 (br s, 1H), 8.50 (s, 1H), 8.20 (br t, 1H, J=5.1 Hz), 7.67 (s, 1H), 7.33-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.20 (s, 2H), 4.09 (d, 1H, J = 13.7 Hz), 3.97 (d, 1H, J = 13.7 Hz), 3.64-3.55 (m, 1H), 3.38-3.32 (m, 1H), 3.11-3.04 (m, 2H), 1.88 (s, 3H), 1.10 (s, 3H, J=7.2 Hz), 0.98 (s, 3H, J=7.2 Hz).
250		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.79 (br s, 1H), 8.81 (s, 1H), 7.23-7.16 (m, 2H), 6.94-6.90 (m, 1H), 4.99-4.95 (m, 1H), 4.80-4.74 (m, 1H), 4.45 (s, 2H), 3.86-3.83 (m, 1H), 3.83 (s, 3H), 3.76 (dd, 1H, J=13.9, 1.4 Hz), 3.63 (dd, 1H, J=10.3, 5.8 Hz), 3.57 (dd, 1H, J=10.3, 7.7 Hz), 3.25 (s, 3H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz).
251		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (br s, 1H), 8.79 (s, 1H), 7.38 (dd, 1H, J=8.5, 6.5 Hz), 7.02 (td, 1H, 8.5, 2.8 Hz), 6.81 (dd, 1H, J=8.5, 2.8 Hz), 4.98-4.94 (m, 1H), 4.78-4.64 (m, 1H), 4.60 (s, 2H), 3.83 (dd, 1H, J=13.7, 4.0 Hz), 3.75 (dd, 1H, J=13.7, 1.4 Hz), 3.62 (dd, 1H, J=10.3, 5.8 Hz), 3.57 (dd, 1H, J=10.3, 7.7 Hz), 3.25 (s, 3H), 2.06-1.99 (m, 1H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz), 0.90-0.84 (m, 2H), 0.66-0.63 (m, 2H).

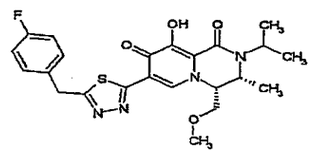
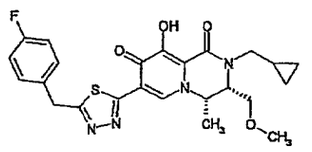
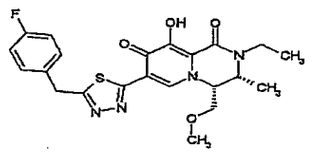
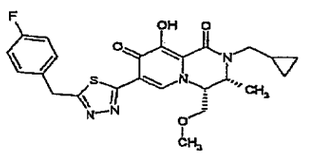
[0487]

[Table 1-71]

No.	structural formula	salt	^{1}H-NMR
252		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.40 (br s, 1H), 8.52 (s, 1H), 8.09-8.05 (m, 1H), 7.65 (s, 1H), 7.34-7.29 (m, 2H), 7.16-7.10 (m, 2H), 4.67 (d, 1H, J=13.5 Hz), 4.37 (d, 1H, J=13.5 Hz), 4.19 (s, 2H), 3.76-3.68 (m, 1H), 3.38-3.29 (m, 1H), 2.54 (d, 3H, J=4.4 Hz), 1.65 (s, 3H), 1.51 (t, 3H, J=7.1 Hz).
253		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.40 (br s, 1H), 8.68 (s, 1H), 7.66 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.86 (d, 1H, J=14.1 Hz), 4.46 (d, 1H, J=14.1 Hz), 4.19 (s, 2H), 3.78-3.69 (m, 1H), 3.18-3.09 (m, 1H), 2.99 (br s, 6H), 1.71 (s, 3H), 1.19 (t, 3H, J=7.1 Hz).
254		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.42 (br s, 1H), 8.69 (s, 1H), 7.65 (s, 1H), 7.34-7.29 (m, 2H), 7.16-7.11 (m, 2H), 4.86 (d, 1H, J=13.9 Hz), 4.46 (d, 1H, J=13.9 Hz), 4.30-4.03 (m, 1H), 4.19 (s, 2H), 3.78-3.68 (m, 2H), 3.46-3.17 (m, 3H), 1.98-1.78 (m, 4H), 1.73 (s, 3H), 1.17 (t, 3H, J=7.1 Hz).
255		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.70 (br s, 1H), 8.61 (s, 1H), 7.70 (s, 1H), 7.35-7.32 (m, 2H), 7.17-7.13 (m, 2H), 4.21 (s, 2H), 4.21-4.17 (m, 1H), 4.11 (d, 1H, J=13.7 Hz), 3.96 (d, 1H, J=13.7 Hz), 3.89-3.82 (m, 2H), 3.78-3.73 (m, 1H), 3.46 (dd, 1H, J=13.9, 6.9 Hz), 3.25 (dd, 1H, J=13.9, 7.5 Hz), 2.14-2.06 (m, 2H), 1.94 (s, 3H), 1.09-1.03 (m, 1H), 0.52-0.49 (m, 2H), 0.34-0.31 (m, 2H).

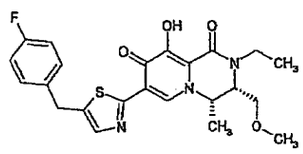
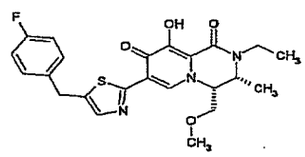
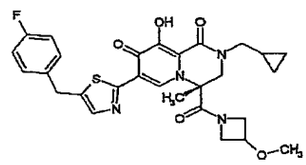
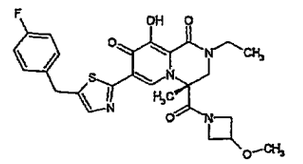
[0488]

[Table 1-72]

No.	structural formula	salt	^{1}H-NMR
256		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.77 (br s, 1H), 8.78 (s, 1H), 7.42-7.39 (m, 2H), 7.20-7.16 (m, 2H), 4.72-4.70 (m, 1H), 4.60-4.53 (m, 1H), 4.47 (s, 2H), 4.18-4.10 (m, 2H), 3.94 (dd, 1H, J=11.9, 2.2 Hz), 3.46 (s, 3H), 1.29 (d, 3H, J=6.9 Hz), 1.27 (d, 3H, J=6.9 Hz), 1.05 (d, 3H, J=6.5 Hz).
257		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.76 (br s, 1H), 8.62 (s, 1H), 7.42-7.38 (m, 2H), 7.20-7.16 (m, 2H), 4.77-4.74 (m, 1H), 4.47 (s, 2H), 4.19 (q, 1H, J=4.0 Hz), 3.71 (dd, 1H, J=14.1, 7.3 Hz), 3.62 (d, 2H, J=4.4 Hz), 3.23 (dd, 1H, J=14.1, 6.9 Hz), 3.16 (s, 3H), 1.69 (d, 3H, J=6.9 Hz), 1.22-1.16 (m, 1H), 0.58-0.48 (m, 2H), 0.44-0.39 (m, 1H), 0.34-0.29 (m, 1H).
258		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.82 (br s, 1H), 8.72 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.84-4.79 (m, 1H), 4.47 (s, 2H), 4.26-4.21 (m, 1H), 3.89-3.76 (m, 3H), 3.33 (s, 3H), 3.33-3.26 (m, 1H), 1.24 (d, 3H, J=6.9 Hz), 1.17 (t, 3H, J=7.3 Hz).
259		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.78 (br s, 1H), 8.74 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.85-4.81 (m, 1H), 4.47 (s, 2H), 4.30-4.24 (m, 1H), 3.93 (dd, 1H, J=11.5, 8.5 Hz), 3.85 (dd, 1H, J=11.5, 3.0 Hz), 3.56 (dd, 1H, J=14.1, 7.5 Hz), 3.37 (s, 3H), 3.30 (dd, 1H, J=14.1, 6.9 Hz), 1.24 (d, 3H, J=6.9 Hz), 1.15-1.09 (m, 1H), 0.58-0.48 (m, 2H), 0.41-0.30 (m, 2H).

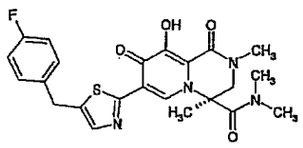
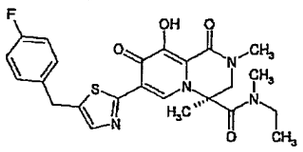
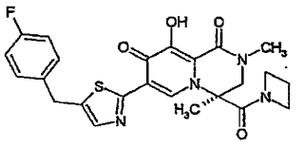
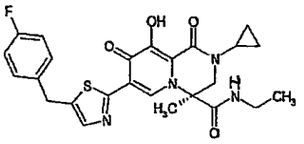
[0489]

[Table 1-73]

No.	structural formula	salt	^{1}H-NMR
260		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.67 (br s, 1H), 8.53 (s, 1H), 7.69 (s, 1H), 7.33-7.29 (m, 2H), 7.17-7.11 (m, 2H), 4.73-4.67 (m, 1H), 4.19 (s, 2H), 4.10 (q, 1H, J=4.1 Hz), 3.90-3.83 (m, 1H), 3.56 (d, 2H, J=4.6 Hz), 3.33-3.32 (m, 1H), 3.16 (s, 3H), 1.61 (d, 3H, J=6.5 Hz), 1.20 (t, 3H, J=7.1 Hz).
261		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.69 (br s, 1H), 8.59 (s, 1H), 7.67 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.79-4.75 (m, 1H), 4.22-4.19 (m, 1H), 4.19 (s, 2H), 3.85-3.73 (m, 3H), 3.31 (s, 3H), 3.31-3.24 (m, 1H), 1.22 (d, 3H, J=6.7 Hz), 1.15 (t, 3H, J=7.1 Hz).
262		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.71 (br s, 1H), 8.60 (s, 1H), 7.70 (s, 1H), 7.35-7.31 (m, 2H), 7.16-7.12 (m, 2H), 4.41-4.38 (m, 1H), 4.20 (s, 2H), 4.10-4.02 (m, 4H), 3.98 (d, 1H, J=13.7 Hz), 3.68-3.59 (m, 1H), 3.43-3.35 (m, 1H), 3.32-3.26 (m, 1H), 3.13 (s, 3H), 1.94 (s, 3H), 1.07-1.00 (m, 1H), 0.53-0.45 (m, 2H), 0.34-0.28 (m, 2H).
263		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.69 (br s, 1H), 8.60 (s, 1H), 7.69 (s, 1H), 7.34-7.31 (m, 2H), 7.14 (br t, 2H, J=8.8 Hz), 4.39-4.36 (m, 1H), 4.20 (s, 2H), 4.11-3.90 (m, 5H), 3.69-3.65 (m, 1H), 3.57-3.40 (m, 2H), 3.12 (s, 3H), 1.92 (s, 3H), 1.09 (t, 3H, J=6.6 Hz).

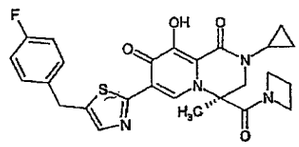
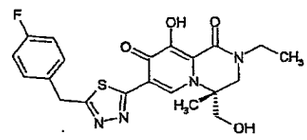
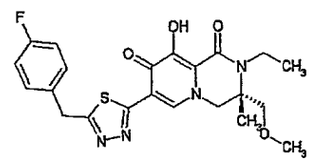
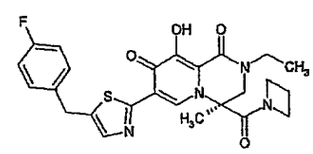
[0490]

[Table 1-74]

No.	structural formula	salt	^{1}H-NMR
264		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (s, 1H), 8.41 (s, 1H), 7.68 (s, 1H), 7.32 (dd, 2H, J=8.2, 5.9 Hz), 7.16-7.13 (m, 2H), 4.19 (s, 2H), 4.18 (d, 1H, J = 13.9 Hz), 3.90 (d, 1H, J = 13.9 Hz), 3.05 (s, 3H), 2.88 (s, 6H), 1.91 (s, 3H).
265		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (s, 1H), 8.40 (s, 1H), 7.67 (s, 1H), 7.35-7.29 (m, 2H), 7.16-7.11 (m, 2H), 4.19 (s, 2H), 4.17 (d, 1H, J = 13.9 Hz), 3.89 (d, 1H, J = 13.9 Hz), 3.43-3.35 (m, 1H), 3.28-3.19 (m, 1H), 3.05 (s, 3H), 2.83 (s, 3H), 1.89 (s, 3H), 0.98 (t, 3H, J=7.1 Hz).
266		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.66 (br s, 1H), 8.62 (s, 1H), 7.70 (s, 1H), 7.34-7.31 (m, 2H), 7.16-7.12 (m, 2H), 4.20 (s, 2H), 4.18-4.11 (m, 1H), 4.04-3.97 (m, 1H), 3.91-3.82 (m, 2H), 3.28-3.19 (m, 1H), 3.64-3.57 (m, 1H), 3.03 (s, 3H), 2.09-2.03 (m, 2H), 1.90 (s, 3H).
267		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.73 (br s, 1H), 8.50 (s, 1H), 8.18 (br t, 1H, J=5.6 Hz), 7.67 (s, 1H), 7.34-7.29 (m, 2H), 7.17-7.11 (m, 2H), 4.20 (s, 2H), 3.99 (d, 1H, J=13.7 Hz), 3.93 (d, 1H, J=13.7 Hz), 3.08-3.01 (m, 2H), 2.87-2.84 (m, 1H), 1.87 (s, 3H), 0.96 (t, 3H, J=7.2 Hz), 0.94-0.89 (m, 1H), 0.81-0.69 (m, 2H), 0.62-0.56 (m, 1H).

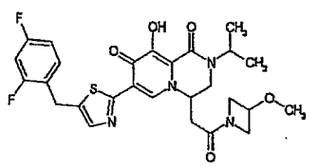
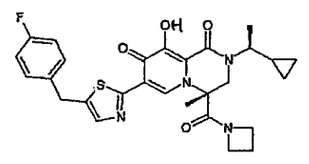
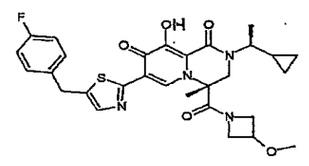
[0491]

[Table 1-75]

No.	structural formula	salt	^{1}H-NMR
268		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.70 (br s, 1H), 8.61 (s, 1H), 7.69 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.20 (s, 2H), 4.07-4.01 (m, 1H), 3.92 (d, 1H, J=13.2 Hz), 3.87-3.82 (m, 2H), 3.80 (d, 1H, J=13.2 Hz), 3.50-3.42 (m, 1H), 2.89-2.84 (m, 1H), 2.08-2.00 (m, 2H), 1.89 (s, 3H), 0.91-0.85 (m, 1H), 0.82-0.73 (m, 2H), 0.67-0.61 (m, 1H).
269		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.18 (br s, 1H), 8.67 (s, 1H), 7.42-7.38 (m, 2H), 7.20-7.14 (m, 2H), 4.46 (s, 2H), 3.83 (d, 1H, J=13.7 Hz), 3.74 (d, 1H, J=13.7 Hz), 3.64 (d, 1H, J=11.8 Hz), 3.62 (d, 1H, J=11.8 Hz), 3.60-3.44 (m, 3H), 1.59 (s, 3H), 1.15 (t, 3H, J=7.2 Hz).
270		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.69 (br s, 1H), 8.75 (s, 1H), 7.41-7.38 (m, 2H), 7.20-7.15 (m, 2H), 4.53 (d, 1H, J=13.7 Hz), 4.46 (s, 2H), 4.30 (d, 1H, J=13.7 Hz), 3.68-3.59 (m, 1H), 3.51 (d, 1H, J=10.4 Hz), 3.48-3.43 (m, 2H), 3.20 (s, 3H), 1.35 (s, 3H), 1.19 (t, 3H, J=7.1 Hz).
271		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.69 (br s, 1H), 8.61 (s, 1H), 7.69 (s, 1H), 7.34-7.31 (m, 2H), 7.16-7.12 (m, 2H), 4.20 (s, 2H), 4.17-4.15 (m, 1H), 4.02 (d, 1H, J=13.5 Hz), 4.00-3.87 (m, 2H), 3.89 (d, 1H, J=13.5 Hz), 3.65-3.63 (m, 1H), 3.54-3.44 (m, 2H), 2.10-2.06 (m, 2H), 1.91 (s, 3H), 1.10 (t, 3H, J=7.1 Hz).

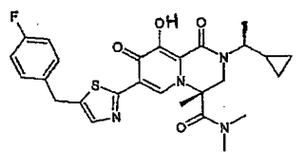
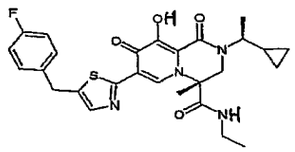
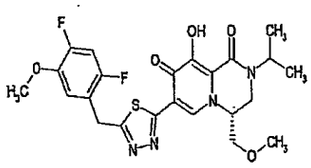
[0492]

[Table 1-76]

No.	structural formula	salt	^{1}H-NMR
272		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.65 (br s, 1H), 8.66 (s, 1H), 7.64 (s, 1H), 7.47–7.41 (m, 1H), 7.24 (dt, 1H, J=14.0, 5.0 Hz), 7.06 (td, 1H, J=8.5, 2.3 Hz), 5.10–5.03 (m, 1H), 4.80–4.73 (m, 1H), 4.20 (s, 2H), 4.18–4.04 (m, 2H), 3.98–3.85 (m, 1H), 3.87–3.71 (m, 3H), 3.61–3.53 (m, 1H), 3.15 (s, 1.5H), 3.08 (s, 1.5H), 2.66–2.58 (m, 2H), 1.15–1.11 (m, 6H).
273		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.83 (br s, 1H), 8.59 (s, 1H), 7.70 (s, 1H), 7.35–7.32 (m, 2H), 7.17–7.13 (m, 2H), 4.21 (s, 2H), 4.21–4.17 (m, 1H), 4.14 (d, 1H, J=13.7 Hz), 3.93–3.76 (m, 5H), 2.16–2.08 (m, 2H), 1.97 (s, 3H), 1.24 (d, 3H, J=6.8 Hz), 1.13–1.10 (m, 1H), 0.64–0.58 (m, 1H), 0.43–0.38 (m, 2H), 0.20–0.15 (m, 1H).
274		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.81 (br s, 1H), 8.58 (s, 1H), 7.70 (s, 1H), 7.35–7.32 (m, 2H), 7.17–7.13 (m, 2H), 4.21 (s, 2H), 4.21–4.14 (m, 3H), 4.06–4.00 (m, 1H), 3.87–3.64 (m, 4H), 3.15 (s, 3H), 1.98 (s, 3H), 1.24 (d, 3H, J=6.6 Hz), 1.13–1.09 (m, 1H), 0.61–0.57 (m, 1H), 0.49–0.36 (m, 2H), 0.15–0.07 (m, 1H).

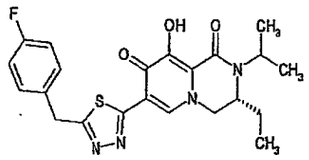
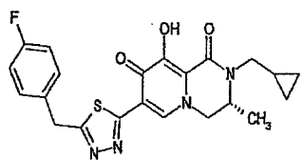
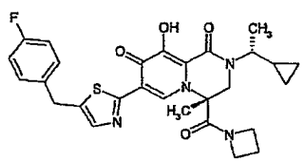
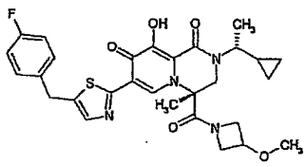
[0493]

[Table 1-77]

No.	structural formula	salt	^{1}H-NMR
275		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.84 (br s, 1H), 8.48 (s, 1H), 7.69 (s, 1H), 7.35–7.32 (m, 2H), 7.17–7.13 (m, 2H), 4.31 (d, 1H, J=14.3 Hz), 4.21 (s, 2H), 3.93 (d, 1H, J=14.3 Hz), 3.83–3.75 (m, 1H), 2.98 (br s, 6H), 2.05 (s, 3H), 1.25 (d, 3H, J=6.8 Hz), 1.10–1.03 (m, 1H), 0.64–0.58 (m, 1H), 0.42–0.33 (m, 2H), 0.12–0.08 (m, 1H).
276		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.86 (br s, 1H), 8.52 (s, 1H), 8.21 (t, 1H, J=5.4 Hz), 7.69 (s, 1H), 7.36–7.31 (m, 2H), 7.18–7.13 (m, 2H), 4.29 (d, 1H, J=13.7 Hz), 4.21 (s, 2H), 3.87 (d, 1H, J=13.7 Hz), 3.81–3.73 (m, 1H), 3.20–3.14 (m, 1H), 3.02–2.96 (m, 1H), 1.94 (s, 3H), 1.24 (d, 3H, J=6.8 Hz), 1.13–1.07 (m, 1H), 1.01 (t, 3H, J=7.2 Hz), 0.62–0.57 (m, 1H), 0.37–0.31 (m, 2H), 0.18–0.12 (m, 1H).
277		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.82 (br s, 1H), 8.80 (s, 1H), 7.38–7.32 (m, 2H), 4.99–4.97 (m, 1H), 4.80–4.74 (m, 1H), 4.46 (s, 2H), 3.84 (dd, 1H, J=13.5, 4.2 Hz), 3.83 (s, 3H), 3.75 (dd, 1H, J=13.5, 1.2 Hz), 3.63 (dd, 1H, J=10.3, 5.8 Hz), 3.57 (dd, 1H, J=10.3, 7.7 Hz), 3.25 (s, 3H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz).

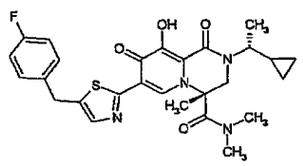
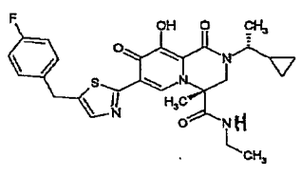
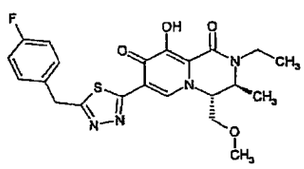
[0494]

[Table 1-78]

No.	structural formula	salt	^{1}H-NMR
278		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.45 (br s, 1H), 8.98 (s, 1H), 7.43–7.38 (m, 2H), 7.21–7.16 (m, 2H), 4.71–4.67 (m, 1H), 4.56–4.49 (m, 1H), 4.47 (s, 2H), 4.30–4.25 (m, 1H), 3.93–3.90 (m, 1H), 1.65–1.61 (m, 1H), 1.46–1.38 (m, 1H), 1.29 (d, 3H, J=2.4 Hz), 1.27 (d, 3H, J=2.0 Hz), 0.92 (t, 3H, J=7.5 Hz).
279		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.60 (br s, 1H), 8.84 (s, 1H), 7.43–7.38 (m, 2H), 7.20–7.15 (m, 2H), 4.50–4.46 (m, 1H), 4.46 (s, 2H), 4.41 (dd, 1H, J=13.1, 3.6 Hz), 4.20–4.17 (m, 1H), 3.57 (dd, 1H, J=14.0, 7.1 Hz), 3.22 (dd, 1H, J=14.0, 7.0 Hz), 1.24 (d, 3H, J=6.5 Hz), 1.14–1.10 (m, 1H), 0.56–0.47 (m, 2H), 0.39–0.36 (m, 1H), 0.33–0.29 (m, 1H).
280		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.75 (br s, 1H), 8.61 (s, 1H), 7.70 (s, 1H), 7.35–7.32 (m, 2H), 7.18–7.13 (m, 2H), 4.21 (s, 2H), 4.21–4.13 (m, 2H), 3.86–3.73 (m, 5H), 2.14–2.06 (m, 2H), 1.96 (s, 3H), 1.20 (d, 3H, J=6.6 Hz), 1.15–1.07 (m, 1H), 0.64–0.58 (m, 1H), 0.45–0.38 (m, 2H), 0.23–0.20 (m, 1H).
281		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.74 (br s, 1H), 8.60 (s, 1H), 7.70 (s, 1H), 7.36–7.32 (m, 2H), 7.17–7.13 (m, 2H), 4.21 (s, 2H), 4.15–4.04 (m, 4H), 3.89–3.78 (m, 2H), 3.68–3.58 (m, 2H), 3.15 (s, 1.5H), 3.14 (s, 1.5H), 1.98 (s, 3H), 1.19–1.11 (m, 4H), 0.61–0.57 (m, 1H), 0.49–0.38 (m, 2H), 0.22–0.19 (m, 1H).

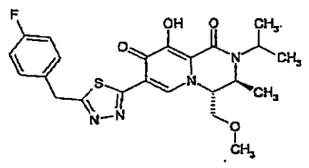
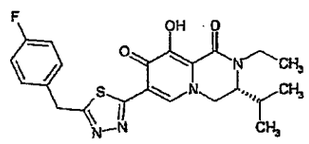
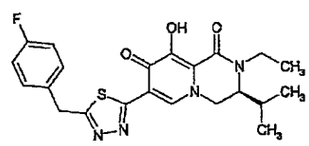
[0495]

[Table 1-79]

No.	structural formula	salt	^{1}H-NMR
282		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.84 (br s, 1H), 8.42 (s, 1H), 7.69 (s, 1H), 7.35–7.32 (m, 2H), 7.18–7.12 (m, 2H), 4.24 (d, 1H, J=14.3 Hz), 4.21 (s, 2H), 3.93 (d, 1H, J=14.3 Hz), 3.89–3.81 (m, 1H), 2.94 (br s, 6H), 1.99 (s, 3H), 1.19 (d, 3H, J=6.6 Hz), 1.15–1.09 (m, 1H), 0.63–0.58 (m, 1H), 0.48–0.39 (m, 2H), 0.26–0.22 (m, 1H).
283		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.77 (br s, 1H), 8.53 (s, 1H), 8.25 (t, 1H, J=5.4 Hz), 7.69 (s, 1H), 7.35–7.32 (m, 2H), 7.17–7.13 (m, 2H), 4.29 (d, 1H, J=13.9 Hz), 4.21 (s, 2H), 3.92 (d, 1H, J=13.9 Hz), 3.89–3.83 (m, 1H), 3.16–3.02 (m, 2H), 1.95 (s, 3H), 1.18 (d, 3H, J=6.8 Hz), 1.03–1.01 (m, 1H), 1.01 (t, 3H, J=7.2 Hz), 0.62–0.58 (m, 1H), 0.47–0.39 (m, 2H), 0.24–0.19 (m, 1H).
284		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.66 (br s, 1H), 8.82 (s, 1H), 7.43–7.39 (m, 2H), 7.21–7.16 (m, 2H), 4.83 (br t, 1H, J=6.6 Hz), 4.48 (s, 2H), 4.04 (q, 1H, J=6.2 Hz), 3.95–3.86 (m, 1H), 3.64 (dd, 1H, J=10.4, 5.3 Hz), 3.53 (dd, 1H, J=10.4, 7.9 Hz), 3.24 (s, 3H), 3.16–3.07 (m, 1H), 1.26 (d, 3H, J=6.6 Hz), 1.16 (t, 3H, J=7.1 Hz).

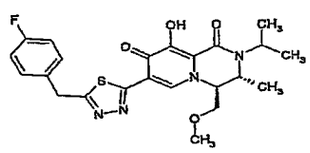
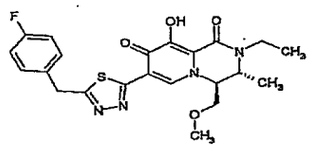
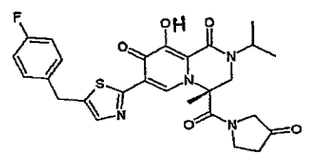
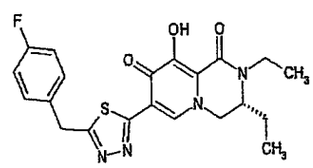
[0496]

[Table 1-80]

No.	structural formula	salt	^{1}H-NMR
285		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.67 (br s, 1H), 8.82 (s, 1H), 7.43-7.39 (m, 2H), 7.22-7.15 (m, 2H), 4.82 (br t, 1H, J=6.0 Hz), 4.65-4.58 (m, 1H), 4.48 (s, 2H), 4.16 (q, 1H, J=6.5 Hz), 3.60 (dd, 1H, J=10.3, 5.4 Hz), 3.49 (dd, 1H, J=10.3, 7.9 Hz), 3.24 (s, 3H), 1.27 (d, 3H, J=2.0 Hz), 1.26 (d, 3H, J=2.0 Hz), 1.21 (t, 3H, J=6.8 Hz).
286		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.53 (br s, 1H), 9.01 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.15 (m, 2H), 4.75 (d, 1H, J=13.8 Hz), 4.47 (s, 2H), 4.34 (dd, 1H, J=13.8, 4.3 Hz), 4.01 (td, 1H, J=13.8, 6.9 Hz), 3.74 (br t, 1H, J=5.0 Hz), 3.74 (td, 1H, J=13.8, 6.9 Hz), 1.92 (td, 1H, J=13.8, 6.9 Hz), 1.20 (t, 3H, J = 6.9 Hz), 0.99 (d, 3H, J=6.9 Hz), 0.79 (d, 3H, J=6.9 Hz).
287		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.53 (br s, 1H), 9.01 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.15 (m, 2H), 4.75 (d, 1H, J=13.8 Hz), 4.47 (s, 2H), 4.34 (dd, 1H, J=13.8, 4.3 Hz), 4.01 (td, 1H, J=13.8, 6.9 Hz), 3.74 (br t, 1H, J=5.0 Hz), 3.74 (td, 1H, J=13.8, 6.9 Hz), 1.92 (td, 1H, J=13.8, 6.9 Hz), 1.20 (t, 3H, J = 6.9 Hz), 0.99 (d, 3H, J=6.9 Hz), 0.79 (d, 3H, J=6.9 Hz).

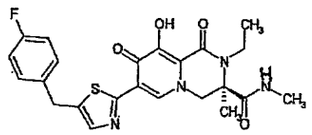
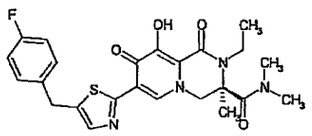
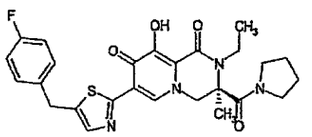
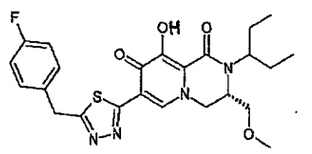
[0497]

[Table 1-81]

No.	structural formula	salt	^{1}H-NMR
288		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.67 (br s, 1H), 8.82 (s, 1H), 7.43-7.39 (m, 2H), 7.22-7.15 (m, 2H), 4.82 (br t, 1H, J=6.0 Hz), 4.65-4.58 (m, 1H), 4.48 (s, 2H), 4.16 (q, 1H, J=6.5 Hz), 3.60 (dd, 1H, J=10.3, 5.4 Hz), 3.49 (dd, 1H, J=10.3, 7.9 Hz), 3.24 (s, 3H), 1.27 (d, 3H, J=2.0 Hz), 1.26 (d, 3H, J=2.0 Hz), 1.21 (t, 3H, J=6.8 Hz).
289		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.66 (br s, 1H), 8.82 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.83 (br t, 1H, J=6.6 Hz), 4.48 (s, 2H), 4.04 (q, 1H, J=6.2 Hz), 3.95-3.86 (m, 1H), 3.64 (dd, 1H, J=10.4, 5.3 Hz), 3.53 (dd, 1H, J=10.4, 7.9 Hz), 3.24 (s, 3H), 3.16-3.07 (m, 1H), 1.26 (d, 3H, J=6.6 Hz), 1.16 (t, 3H, J=7.1 Hz).
290		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.86 (br s, 1H), 8.56 (s, 1H), 7.70 (s, 1H), 7.37-7.31 (m, 2H), 7.19-7.12 (m, 2H), 4.73-4.66 (m, 1H), 4.21 (s, 2H), 4.19-4.07 (m, 2H), 3.86-3.70 (m, 6H), 2.03 (s, 3H), 1.17 (d, 3H, J = 6.5 Hz), 1.10 (d, 3H, J=6.5 Hz).
291		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.53 (br s, 1H), 8.96 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.65 (d, 1H, J=13.5 Hz), 4.47 (s, 2H), 4.35 (dd, 1H, J=13.5, 3.8 Hz), 3.92-3.84 (m, 2H), 3.24-3.16 (m, 1H), 1.72-1.66 (m, 1H), 1.51-1.41 (m, 1H), 1.20 (t, 3H, J=7.3 Hz), 0.92 (t, 3H, J=7.5 Hz).

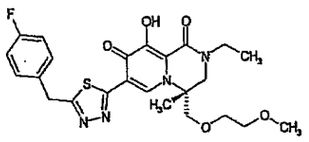
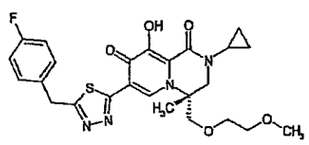
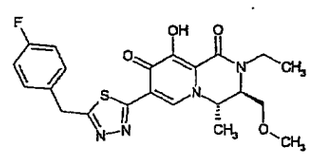
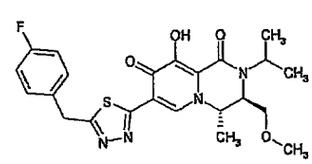
[0498]

[Table 1-82]

No.	structural formula	salt	^{1}H-NMR
292		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.40 (br s, 1H), 8.52 (s, 1H), 8.09-8.05 (m, 1H), 7.65 (s, 1H), 7.34-7.29 (m, 2H), 7.16-7.10 (m, 2H), 4.67 (d, 1H, J=13.5 Hz), 4.37 (d, 1H, J=13.5 Hz), 4.19 (s, 2H), 3.76-3.68 (m, 1H), 3.38-3.29 (m, 1H), 2.54 (d, 3H, J=4.4 Hz), 1.65 (s, 3H), 1.51 (t, 3H, J=7.1 Hz).
293		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.40 (br s, 1H), 8.68 (s, 1H), 7.66 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.86 (d, 1H, J=14.1 Hz), 4.46 (d, 1H, J=14.1 Hz), 4.19 (s, 2H), 3.78-3.69 (m, 1H), 3.18-3.09 (m, 1H), 2.99 (br s, 6H), 1.71 (s, 3H), 1.19 (t, 3H, J=7.1 Hz).
294		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.42 (br s, 1H), 8.69 (s, 1H), 7.65 (s, 1H), 7.34-7.29 (m, 2H), 7.16-7.11 (m, 2H), 4.86 (d, 1H, J=13.9 Hz), 4.46 (d, 1H, J=13.9 Hz), 4.30-4.03 (m, 1H), 4.19 (s, 2H), 3.78-3.68 (m, 2H), 3.46-3.17 (m, 3H), 1.98-1.78 (m, 4H), 1.73 (s, 3H), 1.17 (t, 3H, J=7.1 Hz).
295		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.46 (br s, 1H), 8.84 (s, 1H), 7.43-7.39 (m, 2H), 7.20-7.15 (m, 2H), 4.68 (d, 1H, J=13.5 Hz), 4.46 (s, 2H), 4.36 (dd, 1H, J=13.5, 3.7 Hz), 4.08-4.00 (m, 2H), 3.49 (dd, 1H, J=10.2, 3.9 Hz), 3.41 (dd, 1H, J=10.2, 7.0 Hz), 3.17 (s, 3H), 1.77-1.59 (m, 4H), 0.90 (t, 3H, J=7.3 Hz), 0.85 (t, 3H, J=7.3 Hz).

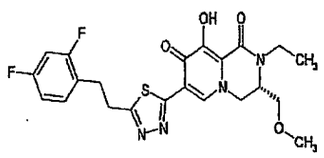
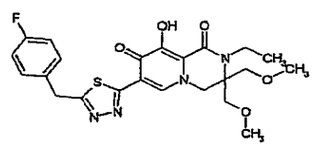
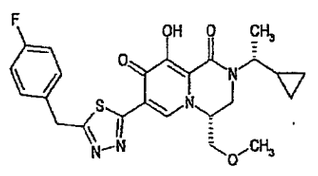
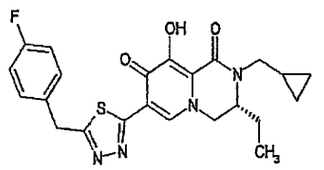
[0499]

[Table 1-83]

No.	structural formula	salt	^{1}H-NMR
296		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.19 (br s, 1H), 8.71 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.47 (s, 2H), 3.86-3.76 (m, 3H), 3.70 (d, 1H, J=10.4 Hz), 3.63-3.45 (m, 4H), 3.35-3.33 (m, 2H), 3.11 (s, 3H), 1.64 (s, 3H), 1.17 (t, 3H, J=7.2 Hz).
297		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.21 (br s, 1H), 8.71 (s, 1H), 7.42-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.47 (s, 2H), 3.80-3.63 (m, 4H), 3.51-3.44 (m, 2H), 3.35-3.33 (m, 2H), 3.12 (s, 3H), 2.95-2.90 (m, 1H), 1.62 (s, 3H), 0.93-0.76 (m, 4H).
298		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.51 (br s, 1H), 8.93 (s, 1H), 7.42-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.91 (q, 1H, J=6.8 Hz), 4.48 (s, 2H), 4.04-3.95 (m, 2H), 3.52 (dd, 1H, J=10.3, 5.2 Hz), 3.46 (dd, 1H, J=10.3, 6.5 Hz), 3.22 (s, 3H), 3.20-3.13 (m, 1H), 1.42 (d, 3H, J=6.6 Hz), 1.19 (t, 3H, J=7.1 Hz).
299		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.48 (br s, 1H), 8.95 (s, 1H), 7.42-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.95 (q, 1H, J=6.5 Hz), 4.58-4.51 (m, 1H), 4.48 (s, 2H), 4.07-4.04 (m, 1H), 3.50 (dd, 1H, J=10.5, 4.1 Hz), 3.36 (dd, 1H, J=10.5, 7.9 Hz), 3.22 (s, 3H), 1.39 (d, 3H, J=6.8 Hz), 1.29 (d, 3H, J=5.0 Hz), 1.27 (d, 3H, J=5.0 Hz).

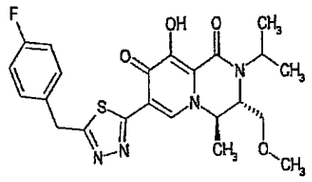
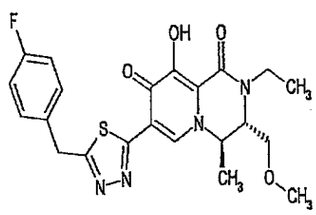
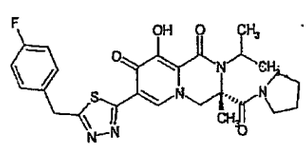
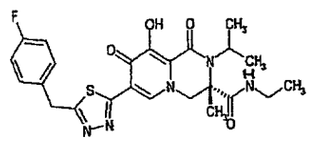
[0500]

[Table 1-84]

No.	structural formula	salt	^{1}H-NMR
300		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.50 (br s, 1H), 8.82 (s, 1H), 7.39 (dd, 1H, J=15.3, 8.7 Hz), 7.22-7.16 (m, 1H), 7.02 (td, 1H, J=8.7, 2.4 Hz), 4.63 (d, 1H, J=13.3 Hz), 4.42 (dd, 1H, J=13.3, 4.3 Hz), 4.17-4.13 (m, 1H), 3.87 (td, 1H, J=14.0, 7.1 Hz), 3.56-3.49 (m, 2H), 3.40 (t, 2H, J=7.5 Hz), 3.32-3.25 (m, 1H), 3.22 (s, 3H), 3.09 (t, 2H, J=7.5 Hz), 1.21 (t, 3H, J=7.1 Hz).
301		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.61 (br s, 1H), 8.78 (s, 1H), 7.42-7.39 (m, 2H), 7.20-7.16 (m, 2H), 4.51 (s, 2H), 4.47 (s, 2H), 3.65-3.53 (m, 6H), 3.26 (s, 6H), 1.19 (t, 3H, J=7.1 Hz).
302		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (br s, 1H), 8.80 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.15 (m, 2H), 4.99-4.95 (m, 1H), 4.46 (s, 2H), 3.99-3.84 (m, 3H), 3.63 (dd, 1H, J=10.3, 5.7 Hz), 3.57 (dd, 1H, J=10.3, 7.7 Hz), 3.24 (s, 3H), 1.22 (d, 3H, J=7.0 Hz), 1.08-1.00 (m, 1H), 0.61-0.55 (m, 1H), 0.47-0.36 (m, 2H), 0.23-0.18 (m, 1H).
303		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.50 (br s, 1H), 8.97 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.69 (d, 1H, J=13.3 Hz), 4.48 (s, 2H), 4.38 (dd, 1H, J=13.3, 3.4 Hz), 3.95-3.93 (m, 1H), 3.69 (dd, 1H, J=13.9, 7.1 Hz), 3.16 (dd, 1H, J=13.9 7.2 Hz), 1.79-1.72 (m, 1H), 1.48-1.40 (m, 1H), 1.19-1.12 (m, 1H), 0.93 (t, 3H, J=7.4 Hz), 0.55-0.48 (m, 2H), 0.42-0.37 (m, 1H), 0.34-0.30 (m, 1H).

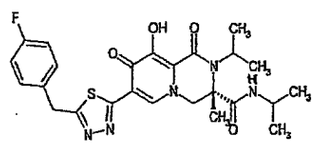
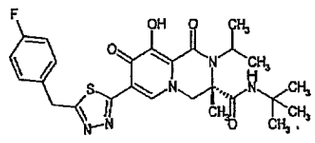
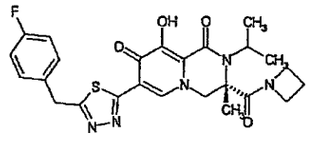
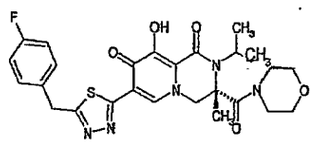
[0501]

[Table 1-85]

No.	structural formula	salt	^{1}H-NMR
304		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.48 (br s, 1H), 8.95 (s, 1H), 7.42-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.95 (q, 1H, J=6.5 Hz), 4.58-4.51 (m, 1H), 4.48 (s, 2H), 4.07-4.04 (m, 1H), 3.50 (dd, 1H, J=10.5, 4.1 Hz), 3.36 (dd, 1H, J=10.5, 7.9 Hz), 3.22 (s, 3H), 1.39 (d, 3H, J=6.8 Hz), 1.29 (d, 3H, J=5.0 Hz), 1.27 (d, 3H, J=5.0 Hz).
305		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.51 (br s, 1H), 8.93 (s, 1H), 7.42-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.91 (q, 1H, J=6.8 Hz), 4.48 (s, 2H), 4.04-3.95 (m, 2H), 3.52 (dd, 1H, J=10.3, 5.2 Hz), 3.46 (dd, 1H, J=10.3, 6.5 Hz), 3.22 (s, 3H), 3.20-3.13 (m, 1H), 1.42 (d, 3H, J=6.6 Hz), 1.19 (t, 3H, J=7.1 Hz).
306		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.70 (br s, 1H), 8.86 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.80 (d, 1H, J = 14.0 Hz), 4.49 (d, 1H, J = 14.0 Hz), 4.47 (s, 2H), 4.11-3.06 (m, 4H), 3.60 (sep, 1H, J = 6.6 Hz), 2.06-1.63 (m, 4H), 1.73 (s, 3H), 1.46 (d, 3H, J = 6.6 Hz), 1.43 (d, 3H, J = 6.6 Hz).
307		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.65 (br s, 1H), 8.74 (s, 1H), 8.31 (t, 1H, J = 5.5 Hz), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.58 (d, 1H, J = 13.5 Hz), 4.48 (d, 1H, J = 13.5 Hz), 4.47 (s, 2H), 3.53 (sep, 1H, J = 6.6 Hz), 3.20-3.09 (m, 2H), 1.58 (s, 3H), 1.48 (d, 3H, J = 6.6 Hz), 1.41 (d, 3H, J = 6.6 Hz), 1.01 (t, 3H, J = 7.2 Hz).

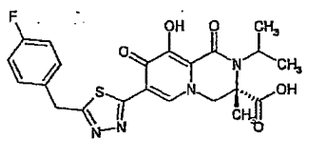
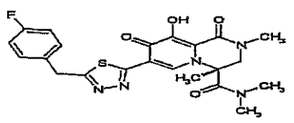
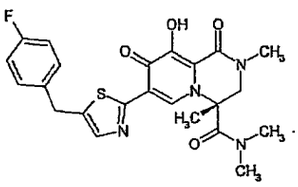
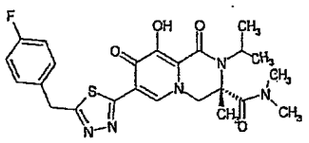
[0502]

[Table 1-86]

No.	structural formula	salt	^{1}H-NMR
308		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.68 (br s, 1H), 8.74 (s, 1H), 8.11 (d, 1H, J = 7.7 Hz), 7.45–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.61 (d, 1H, J = 14.0 Hz), 4.49 (d, 1H, J = 14.0 Hz), 4.47 (s, 2H), 3.91 (sep, 1H, J = 6.6 Hz), 3.48 (sep, 1H, J = 6.6 Hz), 1.55 (s, 3H), 1.51 (d, 3H, J = 6.6 Hz), 1.41 (d, 3H, J = 6.6 Hz), 1.09 (d, 3H, J = 6.6 Hz), 1.06 (d, 3H, J = 6.6 Hz).
309		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.75 (br s, 1H), 8.75 (s, 1H), 7.77 (s, 1H), 7.44–7.37 (m, 2H), 7.22–7.15 (m, 2H), 4.67 (d, 1H, J = 13.5 Hz), 4.49 (d, 1H, J = 13.5 Hz), 4.47 (s, 2H), 3.40 (sep, 1H, J = 6.7 Hz), 1.54 (d, 3H, J = 6.7 Hz), 1.50 (s, 3H), 1.41 (d, 3H, J = 6.7 Hz), 1.29 (s, 9H).
310		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.66 (br s, 1H), 8.85 (s, 1H), 7.44–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.68–3.76 (m, 4H), 4.64 (d, 1H, J = 13.9 Hz), 4.47 (s, 2H), 4.46 (d, 1H, J = 13.9 Hz), 3.69 (sep, 1H, J = 6.7 Hz), 2.28–2.15 (m, 2H), 1.66 (s, 3H), 1.44 (d, 3H, J = 6.7 Hz), 1.43 (d, 3H, J = 6.7 Hz).
311		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.67 (br s, 1H), 8.81 (s, 1H), 7.45–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.71 (d, 1H, J = 14.0 Hz), 4.58 (d, 1H, J = 14.0 Hz), 4.47 (s, 2H), 3.75–3.40 (m, 9H), 1.66 (s, 3H), 1.53 (d, 3H, J = 6.6 Hz), 1.42 (d, 3H, J = 6.6 Hz).

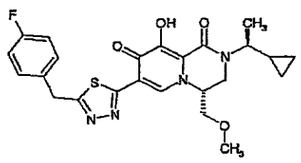
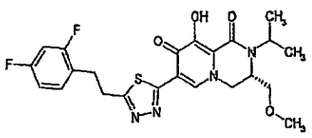
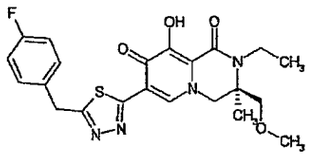
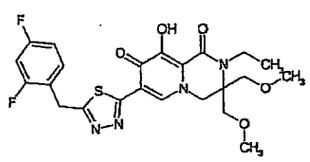
[0503]

[Table 1-87]

No.	structural formula	salt	^{1}H-NMR
312		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.99 (br s, 1H), 12.50 (br s, 1H), 8.83 (s, 1H), 7.45-7.37 (m, 2H), 7.23-7.13 (m, 2H), 4.78 (d, 1H, J = 14.0 Hz), 4.49 (d, 1H, J = 14.0 Hz), 4.47 (s, 2H), 3.85 (sep, 1H, J = 6.8 Hz), 1.66 (s, 3H), 1.49 (d, 3H, J = 6.8 Hz), 1.45 (d, 3H, J = 6.8 Hz).
313		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.88 (br s, 1H), 8.55 (s, 1H), 7.45-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.48 (s, 2H), 4.21 (d, 1H, J = 14.0 Hz), 3.96 (d, 1H, J = 14.0 Hz), 3.07 (s, 3H), 2.91 (s, 6H), 1.98 (s, 3H).
314		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (br s, 1H), 8.42 (s, 1H), 7.69 (s, 1H), 7.36-7.30 (m, 2H), 7.18-7.11 (m, 2H), 4.21 (s, 2H), 4.20 (d, 1H, J = 13.9 Hz), 3.91 (d, 1H, J = 13.9 Hz), 3.07 (s, 3H), 2.89 (s, 6H), 1.92 (s, 3H).
315		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.70 (br s, 1H), 8.84 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.16 (m, 2H), 4.80 (d, 1H, J = 13.9 Hz), 4.53 (d, 1H, J = 13.9 Hz), 4.47 (s, 2H), 3.45 (sep, 1H, J = 6.6 Hz), 3.08 (s, 6H), 1.65 (s, 3H), 1.49 (d, 3H, J = 6.6 Hz), 1.42 (d, 3H, J = 6.6 Hz).

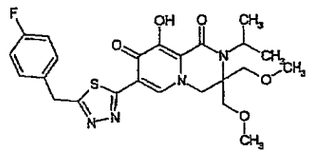
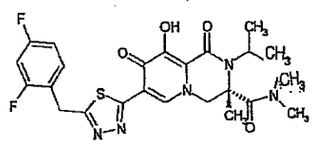
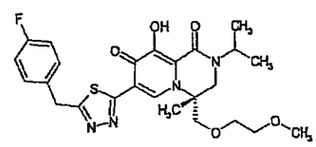
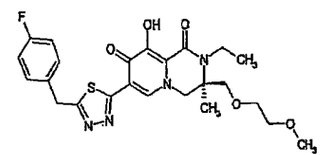
[0504]

[Table 1-88]

No.	structural formula	salt	^{1}H-NMR
316		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.79 (br s, 1H), 8.80 (s, 1H), 7.45–7.39 (m, 2H), 7.23–7.15 (m, 2H), 5.06–4.97 (m, 1H), 4.48 (s, 2H), 3.94–3.91 (m, 2H), 3.90–3.80 (m, 1H), 3.72–3.58 (m, 2H), 3.26 (s, 3H), 1.23 (d, 3H, J = 6.8 Hz), 1.18–1.07 (m, 1H), 0.66–0.57 (m, 1H), 0.50–0.37 (m, 2H), 0.31–0.20 (m, 1H).
317		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.48 (br s, 1H), 8.84 (s, 1H), 7.44–7.36 (m, 1H), 7.23–7.15 (m, 1H), 7.06–6.98 (m, 1H), 4.66 (dd, 1H, J = 13.6, 1.4 Hz), 4.48 (sep, 1H, J = 6.8 Hz), 4.35 (dd, 1H, J = 13.6, 3.6 Hz), 4.24–4.17 (m, 1H), 3.50 (dd, 1H, J = 10.4, 4.2 Hz), 3.44–3.37 (m, 3H), 3.22 (s, 3H), 3.09 (t, 2H, J = 7.5 Hz), 1.30 (d, 3H, J = 6.8 Hz), 1.29 (d, 3H, J = 6.8 Hz).
318		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.71 (br s, 1H), 8.76 (s, 1H), 7.44–7.37 (m, 2H), 7.22–7.15 (m, 2H), 4.55 (d, 1H, J = 13.5 Hz), 4.47 (s, 2H), 4.31 (d, 1H, J = 13.5 Hz), 3.71–3.59 (m, 1H), 3.56–3.42 (m, 3H), 3.21 (s, 3H), 1.37 (s, 3H), 1.20 (t, 3H, J = 7.1 Hz).
319		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.63 (br s, 1H), 8.77 (s, 1H), 7.58–7.48 (m, 1H), 7.33–7.25 (m, 1H), 7.16–7.08 (m, 1H), 4.52 (s, 2H), 4.49 (s, 2H), 3.63 (d, 2H, J = 10.6 Hz), 3.58 (q, 2H, J = 7.1 Hz), 3.54 (d, 2H, J = 10.6 Hz), 3.26 (s, 6H), 1.19 (t, 3H, J = 7.1 Hz).

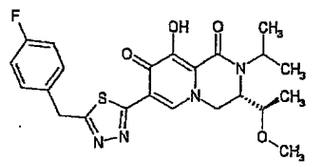
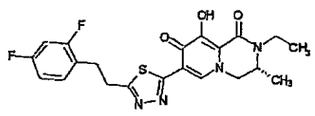
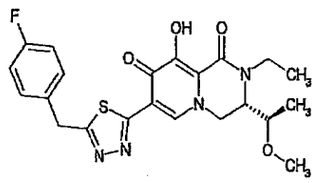
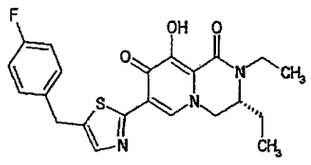
[0505]

[Table 1-89]

No.	structural formula	salt	^{1}H-NMR
320		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.74 (br s, 1H), 8.74 (s, 1H), 7.44–7.37 (m, 2H), 7.22–7.14 (m, 2H), 4.50 (s, 2H), 4.47 (s, 2H), 3.94 (sep, 1H, J = 6.6 Hz), 3.66 (d, 2H, J = 10.6 Hz), 3.51 (d, 2H, J = 10.6 Hz), 3.27 (s, 6H), 1.45 (d, 6H, J = 6.6 Hz).
321		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.71 (br s, 1H), 8.83 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.26 (m, 1H), 7.15–7.08 (m, 1H), 4.80 (d, 1H, J = 14.0 Hz), 4.54 (d, 1H, J = 14.0 Hz), 4.49 (s, 2H), 3.45 (sep, 1H, J = 6.7 Hz), 3.07 (s, 6H), 1.65 (s, 3H), 1.49 (d, 3H, J = 6.7 Hz), 1.42 (d, 3H, J = 6.7 Hz).
322		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.25 (br s, 1H), 8.71 (s, 1H), 7.44–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.79 (sep, 1H, J = 6.8 Hz), 4.47 (s, 2H), 3.80–3.73 (m, 2H), 3.71–3.64 (m, 2H), 3.55–3.43 (m, 2H), 3.37–3.31 (m, 2H), 3.11 (s, 3H), 1.65 (s, 3H), 1.18 (d, 3H, J = 6.8 Hz), 1.18 (d, 3H, J = 6.8 Hz).
323		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.69 (br s, 1H), 8.73 (s, 1H), 7.44–7.38 (m, 2H), 7.23–7.15 (m, 2H), 4.55 (d, 1H, J = 13.5 Hz), 4.47 (s, 2H), 4.31 (d, 1H, J = 13.5 Hz), 3.71–3.46 (m, 4H), 3.46–3.42 (m, 2H), 3.29–3.24 (m, 2H), 3.07 (s, 3H), 1.37 (s, 3H), 1.20 (t, 3H, J = 7.1 Hz).

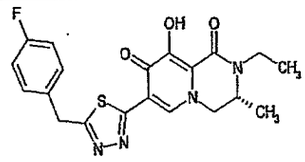
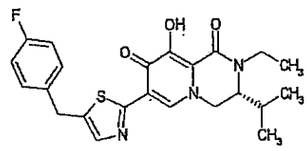
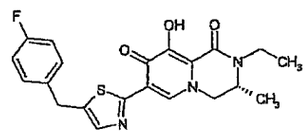
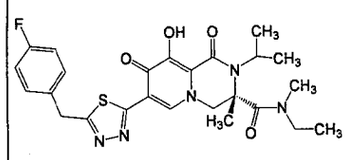
[0506]

[Table 1-90]

No.	structural formula	salt	^{1}H-NMR
324		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.52 (br s, 1H), 8.91 (s, 1H), 7.44-7.36 (m, 2H), 7.22-7.14 (m, 2H), 4.82 (d, 1H, J = 13.5 Hz), 4.47 (s, 2H), 4.35 (sep, 1H, J = 6.8 Hz), 4.30 (dd, 1H, J = 13.5, 4.5 Hz), 4.01-3.96 (m, 1H), 3.64-3.55 (m, 1H), 3.05 (s, 3H), 1.35 (d, 3H, J = 6.8 Hz), 1.33 (d, 3H, J = 6.8 Hz), 1.19 (d, 3H, J = 6.2 Hz).
325		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.64 (br s, 1H), 8.83 (s, 1H), 7.44-7.35 (m, 1H), 7.23-7.15 (m, 1H), 7.05-6.98 (m, 1H), 4.50-4.37 (m, 2H), 4.16-4.07 (m, 1H), 3.88-3.76 (m, 1H), 3.40 (t, 2H, J = 7.5 Hz), 3.30-3.19 (m, 1H), 3.10 (t, 2H, J = 7.5 Hz), 1.24 (d, 3H, J = 6.6 Hz), 1.20 (t, 3H, J = 7.2 Hz).
326		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.50 (br s, 1H), 8.91 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.15 (m, 2H), 4.80 (d, 1H, J = 13.5 Hz), 4.47 (s, 2H), 4.36 (dd, 1H, J = 13.5, 4.6 Hz), 4.00-3.87 (m, 2H), 3.66-3.58 (m, 1H), 3.31-3.18 (m, 1H), 3.08 (s, 3H), 1.21 (t, 3H, J = 7.1 Hz), 1.16 (d, 3H, J = 6.4 Hz).
327		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.42 (br s, 1H), 8.76 (s, 1H), 7.67 (s, 1H), 7.36-7.30 (m, 2H), 7.19-7.11 (m, 2H), 4.61 (d, 1H, J = 13.2 Hz), 4.33 (dd, 1H, J = 13.2, 3.7 Hz), 4.20 (s, 2H), 3.95-3.83 (m, 1H), 3.88-3.80 (m, 1H), 3.22-3.11 (m, 1H), 1.74-1.62 (m, 1H), 1.50-1.36 (m, 1H), 1.20 (t, 3H, J = 7.2 Hz), 0.91 (t, 3H, J = 7.4 Hz).

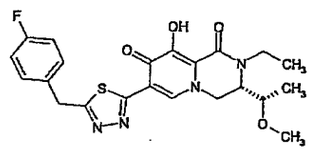
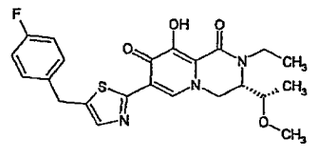
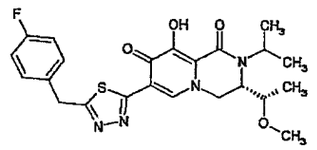
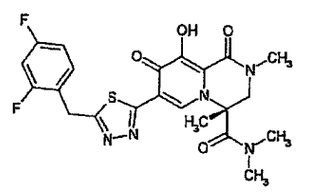
[0507]

[Table 1-91]

No.	structural formula	salt	^{1}H-NMR
328		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.62 (br s, 1H), 8.84 (s, 1H), 7.45-7.37 (m, 2H), 7.23-7.14 (m, 2H), 4.49-4.35 (m, 2H), 4.47 (s, 2H), 4.15-4.07 (m, 1H), 3.87-3.75 (m, 1H), 3.31-3.18 (m, 1H), 1.26-1.14 (m, 6H).
329		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.33 (br s, 1H), 8.82 (s, 1H), 7.67 (s, 1H), 7.37-7.30 (m, 2H), 7.18-7.11 (m, 2H), 4.71 (d, 1H, J = 13.9 Hz), 4.32 (dd, 1H, J = 13.9, 4.4 Hz), 4.20 (s, 2H), 4.07-3.94 (m, 1H), 3.75-3.69 (m, 1H), 3.16-3.04 (m, 1H), 1.97-1.85 (m, 1H), 1.20 (t, 3H, J = 7.1 Hz), 0.98 (d, 3H, J = 6.8 Hz), 0.78 (d, 3H, J = 6.8 Hz).
330		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.52 (br s, 1H), 8.66 (s, 1H), 7.67 (s, 1H), 7.37-7.30 (m, 2H), 7.19-7.11 (m, 2H), 4.46-4.33 (m, 2H), 4.20 (s, 2H), 4.14-4.04 (m, 1H), 3.86-3.75 (m, 1H), 3.29-3.18 (m, 1H), 1.22 (d, 3H, J = 6.6 Hz), 1.19 (t, 3H, J = 7.2 Hz).
331		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.68 (br s, 1H), 8.83 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.77 (d, 1H, J = 13.7 Hz), 4.55 (d, 1H, J = 13.7 Hz), 4.47 (s, 2H), 4.16-3.03 (m, 5H), 3.44 (sep, 1H, J = 6.6 Hz), 1.63 (s, 3H), 1.49 (d, 3H, J = 6.6 Hz), 1.42 (d, 3H, J = 6.6 Hz), 1.09-1.00 (m, 3H).

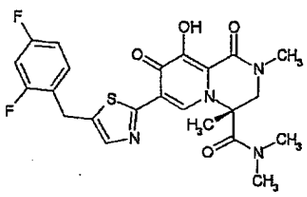
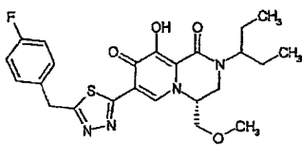
[0508]

[Table 1-92]

No.	structural formula	salt	^{1}H-NMR
332		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.50 (br s, 1H), 8.95 (s, 1H), 7.44–7.36 (m, 2H), 7.22–7.15 (m, 2H), 4.69 (dd, 1H, J = 14.0, 1.5 Hz), 4.47 (s, 2H), 4.39 (dd, 1H, J = 14.0, 4.2 Hz), 4.04–3.98 (m, 1H), 3.97–3.92 (m, 1H), 3.51–3.43 (m, 1H), 3.26–3.18 (m, 1H), 3.18 (s, 3H), 1.19 (t, 3H, J = 7.2 Hz), 1.10 (d, 3H, J = 6.2 Hz).
333		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.76 (s, 1H), 7.67 (s, 1H), 7.36–7.30 (m, 2H), 7.18–7.11 (m, 2H), 4.64 (dd, 1H, J = 13.6, 1.5 Hz), 4.37 (dd, 1H, J = 13.6, 4.0 Hz), 4.20 (s, 2H), 4.06–3.97 (m, 1H), 3.95–3.90 (m, 1H), 3.51–3.40 (m, 1H), 3.27–3.19 (m, 1H), 3.19 (s, 3H), 1.19 (t, 3H, J = 6.8 Hz), 1.08 (d, 3H, J = 6.4 Hz).
334		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.47 (br s, 1H), 8.96 (s, 1H), 7.44–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.68 (dd, 1H, J = 13.9, 1.3 Hz), 4.47 (s, 2H), 4.35 (dd, 1H, J = 13.9, 3.5 Hz), 4.14–4.06 (m, 1H), 3.98–3.93 (m, 1H), 3.41 (sep, 1H, J = 6.7 Hz), 3.24 (s, 3H), 1.39 (d, 3H, J = 6.7 Hz), 1.34 (d, 3H, J = 6.7 Hz), 1.02 (d, 3H, J = 6.3 Hz).
335		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.85 (br s, 1H), 8.54 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.49 (s, 2H), 4.21 (d, 1H, J = 13.9 Hz), 3.97 (d, 1H, J = 13.9 Hz), 3.07 (s, 3H), 2.91 (s, 6H), 1.97 (s, 3H).

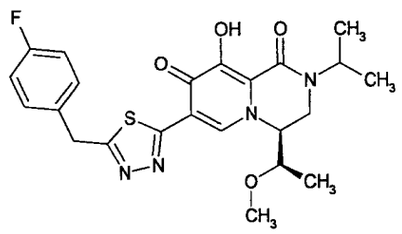
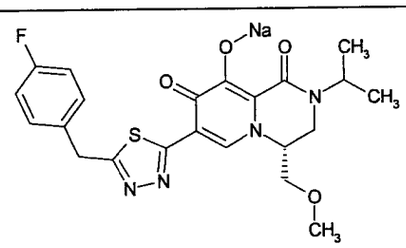
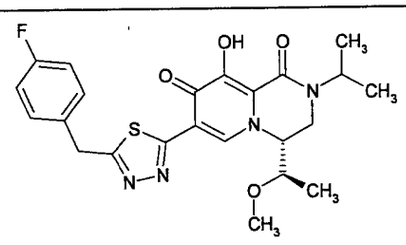
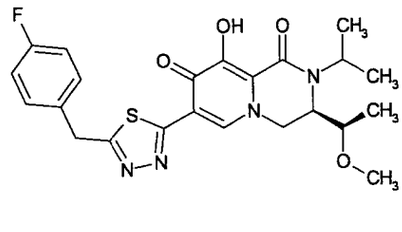
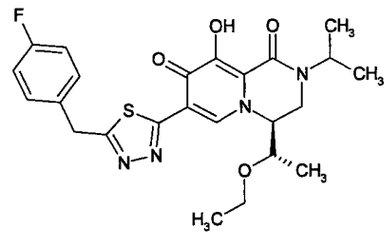
[0509]

[Table 1-93]

No.	structural formula	salt	^{1}H-NMR
336		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.75 (br s, 1H), 8.46 (s, 1H), 7.69 (s, 1H), 7.50-7.42 (m, 1H), 7.29-7.21 (m, 1H), 7.11-7.05 (m, 1H), 4.22 (s, 2H), 4.21 (d, 1H, J = 14.0 Hz), 3.93 (d, 1H, J = 14.0 Hz), 3.07 (s, 3H), 2.89 (s, 6H), 1.93 (s, 3H).
337		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.86 (br s, 1H), 8.83 (s, 1H), 7.45-7.39 (m, 2H), 7.23-7.16 (m, 2H), 5.02-4.94 (m, 1H), 4.47 (s, 2H), 4.40-4.29 (m, 1H), 3.83-3.56 (m, 4H), 3.26 (s, 3H), 1.64-1.43 (m, 4H), 0.92-0.78 (m, 6H).

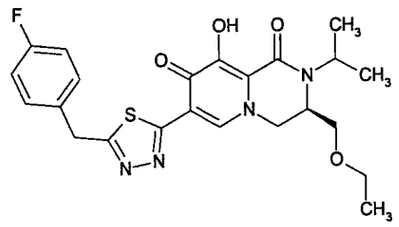
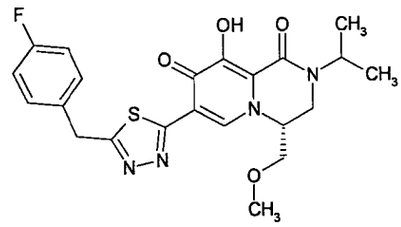
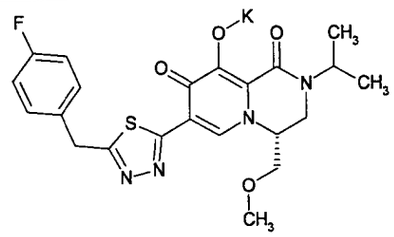
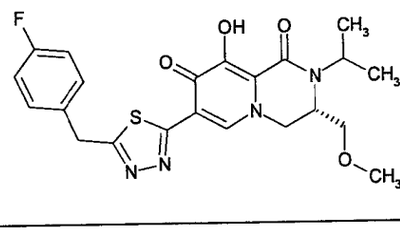
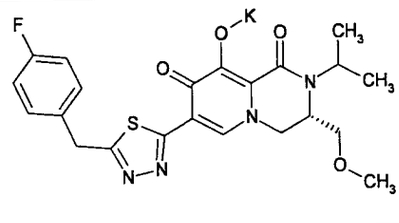
[0510]

[Table 1-94]

No.	structural formula	salt	^{1}H-NMR
338		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.92 (s, 1H), 7.44-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.78 (quint, 1H, J = 6.9 Hz), 4.71 (ddd, 1H, J = 6.4, 4.0, 1.6 Hz), 4.47 (s, 2H), 3.87 (dd, 1H, J = 13.7, 1.6 Hz), 3.78 (dd, 1H, J = 13.7, 4.0 Hz), 3.58 (dq, 1H, J = 6.4, 6.0 Hz), 3.22 (s, 3H), 1.19 (d, 3H, J = 6.9 Hz), 1.17 (d, 3H, J = 6.9 Hz), 1.03 (d, 3H, J = 6.0 Hz).
339			^{1}H-NMR (DMSO-d_6) δ: 8.21 (s, 1H), 7.42-7.39 (m, 2H), 7.20-7.16 (m, 2H), 4.85 (quint, 1H, J = 6.6 Hz), 4.71-4.65 (m, 1H), 4.41 (s, 2H), 3.58-3.53 (m, 3H), 3.48-3.44 (m, 1H), 3.24 (s, 3H), 1.09 (d, 6H, J = 6.6 Hz).
340		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.82 (br s, 1H), 8.72 (s, 1H), 7.44-7.41 (m, 2H), 7.21-7.17 (m, 2H), 4.77 (sep, 1H, J = 6.6 Hz), 4.65 (ddd, 1H, J = 8.2, 4.1, 0.9 Hz), 4.47 (s, 2H), 3.88 (dd, 1H, J = 14.0, 4.1 Hz), 3.76 (dd, 1H, J = 14.0, 0.9 Hz), 3.52 (dq, 1H, J = 8.2, 6.2 Hz), 3.03 (s, 3H), 1.21 (d, 3H, J = 6.2 Hz), 1.20 (d, 3H, J = 6.6 Hz), 1.17 (d, 3H, J = 6.6 Hz).
341		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.95 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.68 (dd, 1H, J = 13.8, 1.5 Hz), 4.47 (s, 2H), 4.35 (dd, 1H, J = 13.8, 3.9 Hz), 4.10 (quint, 1H, J = 6.6 Hz), 3.96 (ddd, 1H, J = 6.6, 3.9, 1.5 Hz), 3.41 (dq, 1H, J = 6.6, 6.4 Hz), 3.24 (s, 3H), 1.39 (d, 3H, J = 6.6 Hz), 1.34 (d, 3H, J = 6.6 Hz), 1.02 (d, 3H, J = 6.4 Hz).
342		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.72 (s, 1H), 7.45-7.41 (m, 3H), 7.22-7.17 (m, 2H), 4.77 (quint, 1H, J = 6.8 Hz), 4.60 (ddd, 1H, J = 8.4, 4.2, 0.9 Hz), 4.47 (s, 2H), 3.88 (dd, 1H, J = 14.3, 4.2 Hz), 3.74 (dd, 1H, J = 14.3, 0.9 Hz), 3.56 (dq, 1H, J = 8.4, 6.2 Hz), 3.41 (dq, 1H, J = 9.5, 7.1 Hz), 2.91 (dq, 1H, J = 9.5, 7.1 Hz), 1.22 (d, 3H, J = 6.2 Hz), 1.20 (d, 3H, J = 6.8 Hz), 1.17 (d, 3H, J = 6.8 Hz), 0.75 (t, 3H, J = 7.1 Hz).

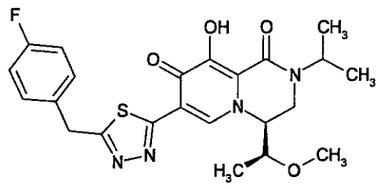
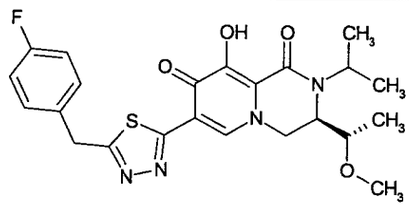
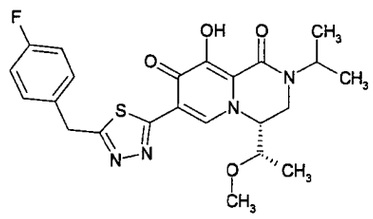
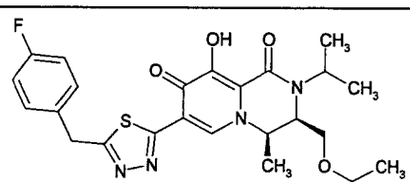
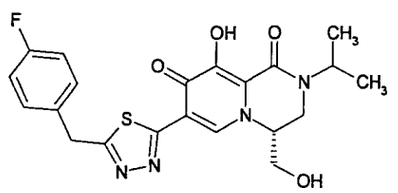
[0511]

[Table 1-95]

No.	structural formula	salt	^{1}H-NMR
343		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.85 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.15 (m, 2H), 4.66 (dd, 1H, J = 12.4, 1.5 Hz), 4.48 (sep, 1H, J = 6.6 Hz), 4.47 (s, 2H), 4.35 (dd, 1H, J = 13.2, 3.7 Hz), 4.20-4.16 (m, 1H), 3.54 (dd, 1H, J = 10.5, 4.1 Hz), 3.45-3.30 (m, 3H), 1.30 (d, 3H, J = 6.6 Hz), 1.28 (d, 3H, J = 6.6 Hz), 0.96 (t, 3H, J = 6.9 Hz).
344			^{1}H-NMR (DMSO-d_6) δ: 12.81 (s, 1H), 8.80 (s, 1H), 7.44-7.39 (m, 2H), 7.22-7.16 (m, 2H), 4.99-4.95 (m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 3.84 (dd, 1H, J = 13.7, 3.9 Hz), 3.75 (dd, 1H, J = 13.9, 1.6 Hz), 3.63 (dd, 1H, J = 10.2, 6.0 Hz), 3.57 (dd, 1H, J = 10.2, 7.7 Hz), 3.25 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
345			^{1}H-NMR (DMSO-d_6) δ: 8.10 (s, 1H), 7.41-7.36 (m, 2H), 7.20-7.14 (m, 2H), 4.83 (quint, 1H, J = 6.7 Hz), 4.62-4.57 (m, 1H), 4.38 (s, 2H), 3.57-3.44 (m, 4H), 3.25 (s, 3H), 1.05 (d, 6H, J = 6.7 Hz).
346			^{1}H-NMR (DMSO-d_6) δ: 12.44 (br s, 1H), 8.85 (s, 1H), 7.44-7.37 (m, 2H), 7.23-7.14 (m, 2H), 4.70-4.61 (m, 1H), 4.54-4.41 (m, 1H), 4.47 (s, 2H), 4.39-4.30 (m, 1H), 4.25-4.14 (m, 1H), 3.53-3.34 (m, 2H), 3.21 (s, 3H), 1.30 (d, 3H, J = 6.3 Hz), 1.28 (d, 3H, J = 6.3 Hz).
347			^{1}H-NMR (DMSO-d_6) δ: 8.02 (br s, 1H), 7.42-7.33 (m, 2H), 7.21-7.13 (m, 2H), 4.73-4.59 (m, 1H), 4.38 (s, 2H), 4.34-4.22 (m, 1H), 4.07-3.96 (m, 1H), 3.89-3.78 (m, 1H), 3.30-3.05 (m, 2H), 3.24 (s, 3H), 1.13 (d, 3H, J = 7.0 Hz), 1.06 (d, 3H, J = 7.0 Hz).

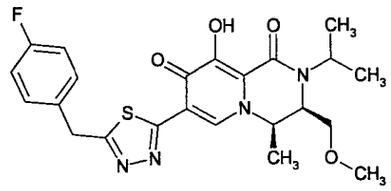
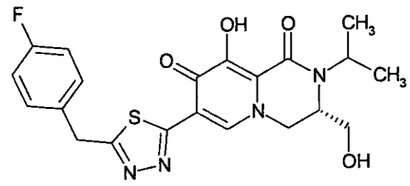
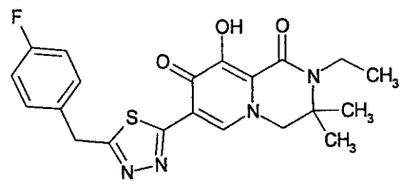
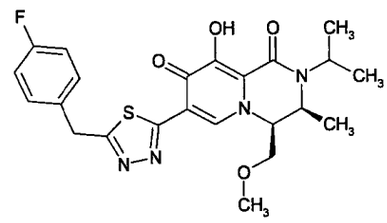
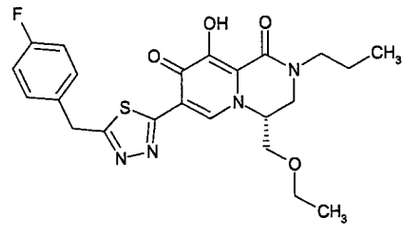
[0512]

[Table 1-96]

No.	structural formula	salt	^{1}H-NMR
348		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.81 (br s, 1H), 8.72 (s, 1H), 7.47-7.37 (m, 2H), 7.23-7.14 (m, 2H), 4.83-4.71 (m, 1H), 4.69-4.60 (m, 1H), 4.47 (s, 2H), 3.88 (dd, 1H, J = 14.1, 3.7 Hz), 3.81-3.71 (m, 1H), 3.56-3.47 (m, 1H), 3.03 (s, 3H), 1.24-1.13 (m, 9H).
349		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.52 (s, 1H), 8.90 (s, 1H), 7.40 (dd, 2H, J = 8.3, 5.6 Hz), 7.17 (dd, 2H, J = 8.3, 8.4 Hz), 4.81 (d, 1H, J = 14.1 Hz), 4.46 (s, 2H), 4.38-4.27 (m, 2H), 3.98 (s, 1H), 3.62-3.56 (m, 1H), 3.04 (s, 3H), 1.33 (t, 6H, J = 6.0 Hz), 1.18 (d, 3H, J = 7.0 Hz).
350		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (s, 1H), 8.91 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.15 (m, 2H), 4.78 (quint, 1H, J = 6.9 Hz), 4.70 (dd, 1H, J = 6.4, 4.2 Hz), 4.47 (s, 2H), 3.86 (d, 1H, J = 13.7 Hz), 3.77 (dd, 1H, J = 13.7, 4.2 Hz), 3.58 (dq, 1H, J = 6.4, 6.0 Hz), 3.21 (s, 3H), 1.19 (d, 3H, J = 6.9 Hz), 1.17 (d, 3H, J = 6.9 Hz), 1.02 (d, 3H, J = 6.0 Hz).
351		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.71 (br s, 1H), 8.56 (s, 1H), 7.44-7.36 (m, 2H), 7.23-7.14 (m, 2H), 4.70-4.60 (m, 1H), 4.50-4.38 (m, 1H), 4.47 (s, 2H), 4.08-4.02 (m, 1H), 3.61 (dd, 1H, J = 11.1, 3.7 Hz), 3.53 (dd, 1H, J = 11.1, 3.9 Hz), 3.27 (q, 2H, J = 7.4 Hz), 1.75 (d, 3H, J = 6.5 Hz), 1.32 (t, 6H, J = 7.0 Hz), 0.82 (t, 3H, J = 7.0 Hz).
352			^{1}H-NMR (DMSO-d_6) δ: 12.79 (br s, 1H), 8.74 (s, 1H), 7.45-7.38 (m, 2H), 7.23-7.15 (m, 2H), 5.32-5.23 (m, 1H), 4.81-4.65 (m, 2H), 4.47 (s, 2H), 3.86-3.64 (m, 3H), 3.60-3.51 (m, 1H), 1.16 (d, 3H, J = 6.7 Hz), 1.15 (d, 3H, J = 6.7 Hz).

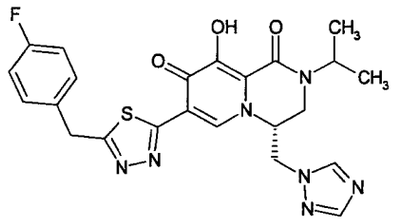
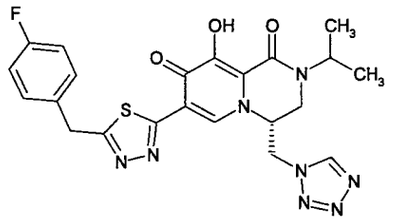
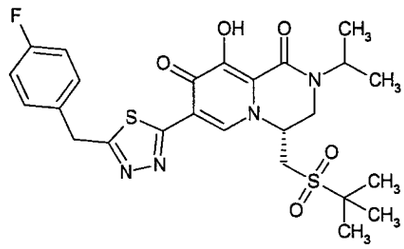
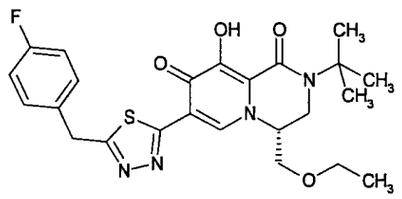
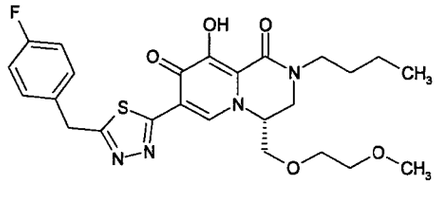
[0513]

[Table 1-97]

No.	structural formula	salt	^{1}H-NMR
353		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (br s, 1H), 8.56 (s, 1H), 7.44-7.36 (m, 2H), 7.23-7.14 (m, 2H), 4.70-4.59 (m, 1H), 4.49-4.37 (m, 1H), 4.47 (s, 2H), 4.11-4.03 (m, 1H), 3.59-3.46 (m, 2H), 3.11 (s, 3H), 1.75 (d, 3H, J = 6.5 Hz), 1.32 (t, 6H, J = 6.5 Hz).
354		HBr	^{1}H-NMR (DMSO-D_6) δ: 8.80 (s, 1H), 7.43-7.37 (m, 2H), 7.21-7.14 (m, 2H), 4.70-4.64 (m, 1H), 4.55-4.44 (m, 3H), 4.33 (dd, 1H, J = 13.3, 3.6 Hz), 3.99-3.93 (m, 1H), 3.56 (dd, 1H, J = 11.4, 3.7 Hz), 3.35 (dd, 1H, J = 11.4, 8.1 Hz), 1.28 (d, 3H, J = 6.7 Hz), 1.27 (d, 3H, J = 6.7 Hz).
355		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.78 (br s, 1H), 8.76 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.14 (m, 2H), 4.47 (s, 2H), 4.34 (s, 2H), 3.55 (q, 2H, J = 7.1 Hz), 1.36 (s, 6H), 1.19 (t, 3H, J = 7.1 Hz).
356		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.76 (s, 1H), 8.77 (s, 1H), 7.42-7.36 (m, 2H), 7.21-7.14 (m, 2H), 4.71 (ddd, 1H, J = 8.0, 2.2, 2.0 Hz), 4.56 (quint, 1H, J = 6.9 Hz), 4.46 (s, 2H), 4.19-4.09 (m, 2H), 3.93 (dd, 1H, J = 11.7, 2.2 Hz), 3.45 (s, 3H), 1.29 (d, 3H, J=6.9 Hz), 1.27 (d, 3H, J=6.9 Hz), 1.04 (d, 3H, J = 6.5 Hz).
357		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.76 (s, 1H), 8.80 (s, 1H), 7.41 (tt, 2H, J = 8.7, 3.1 Hz), 7.18 (tt, 2H, J = 8.9, 2.5 Hz), 4.94-4.88 (m, 1H), 4.46 (s, 2H), 4.06 (dd, 1H, J = 13.8, 4.3 Hz), 3.73-3.67 (m, 2H), 3.64-3.52 (m, 2H), 3.49-3.27 (m, 3H), 1.63-1.53 (m, 2H), 1.01 (t, 3H, J = 7.0 Hz), 0.89 (t, 3H, J = 8.2 Hz).

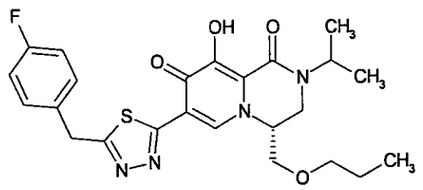
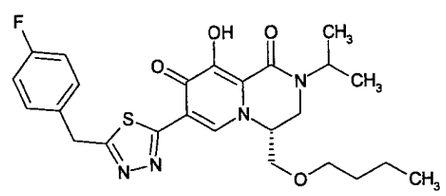
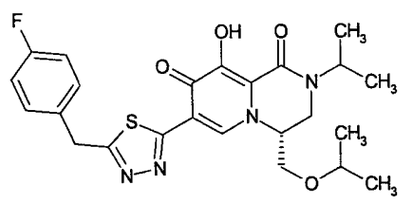
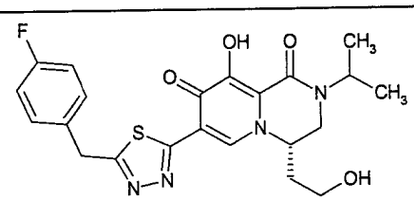
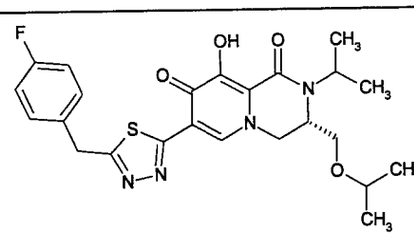
[0514]

[Table 1-98]

No.	structural formula	salt	^{1}H-NMR
358		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.90 (br s, 1H), 8.37 (s, 1H), 8.07 (s, 1H), 8.00 (s, 1H), 7.45-7.37 (m, 2H), 7.23-7.13 (m, 2H), 5.28-5.18 (m, 1H), 4.89-4.60 (m, 3H), 4.44 (s, 2H), 3.98-3.83 (m, 2H), 1.25 (d, 3H, J = 6.7 Hz), 1.18 (d, 3H, J = 6.7 Hz).
359		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.88 (br s, 1H), 8.99 (s, 1H), 8.20 (s, 1H), 7.46-7.37 (m, 2H), 7.24-7.14 (m, 2H), 5.48-5.38 (m, 1H), 5.37-5.19 (m, 2H), 4.84-4.72 (m, 1H), 4.45 (s, 2H), 3.96 (d, 2H, J = 3.0 Hz), 1.25 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz).
360		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.85 (br s, 1H), 8.75 (s, 1H), 7.45-7.37 (m, 2H), 7.22-7.14 (m, 2H), 5.52-5.41 (m, 1H), 4.81-4.71 (m, 1H), 4.47 (s, 2H), 3.98-3.81 (m, 2H), 3.66 (d, 2H, J = 7.0 Hz), 1.29 (s, 9H), 1.21 (d, 3H, J = 6.5 Hz), 1.15 (d, 3H, J = 6.5 Hz).
361		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.94 (s, 1H), 8.80 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.15 (m, 2H), 4.89-4.85 (m, 1H), 4.47 (s, 2H), 3.96 (dd, 1H, J = 14.0, 1.5 Hz), 3.87 (dd, 1H, J = 14.0, 3.0 Hz), 3.70 (dd, 1H, J = 10.2, 6.7 Hz), 3.62 (dd, 1H, J = 10.2, 7.5 Hz), 3.50-3.41 (m, 2H), 1.49 (s, 9H), 1.05 (t, 3H, J = 6.9 Hz).
362		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.80 (s, 1H), 7.44-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.94-4.89 (m, 1H), 4.47 (s, 2H), 4.06 (dd, 1H, J = 13.6, 4.3 Hz), 3.77-3.72 (m, 2H), 3.70-3.46 (m, 5H), 3.38-3.31 (m, 3H), 3.11 (s, 3H), 1.60-1.52 (m, 2H), 1.37-1.27 (m, 2H), 0.92 (t, 3H, J = 7.4 Hz).

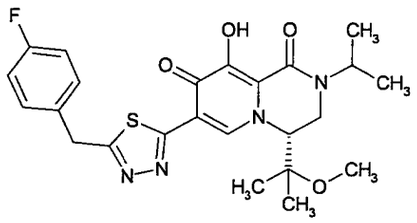
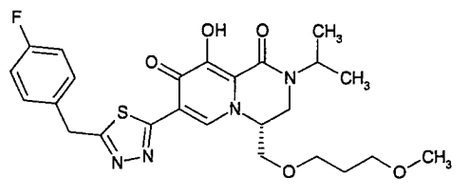
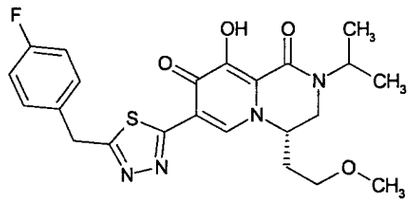
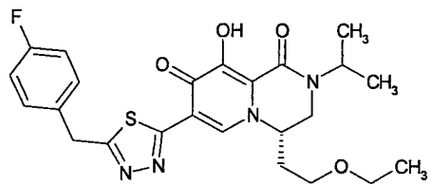
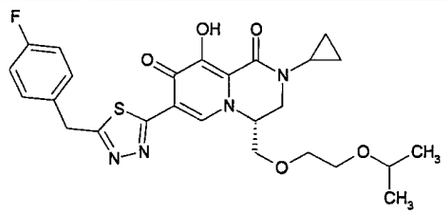
[0515]

[Table 1-99]

No.	structural formula	salt	^{1}H-NMR
363		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.82 (s, 1H), 7.46-7.38 (m, 2H), 7.24-7.14 (m, 2H), 5.01-4.91 (br m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 3.88-3.54 (m, 4H), 3.41-3.24 (m, 2H), 1.41 (td, 2H, J = 13.9, 7.2 Hz), 1.17 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz), 0.74 (t, 3H, J = 7.2 Hz).
364		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.80 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.13 (m, 2H), 4.99-4.89 (m, 1H), 4.76 (sep, 1H, J = 7.0), 4.46 (s, 2H), 3.88-3.52 (m, 4H), 3.43-3.24 (m, 2H), 1.40-1.29 (m, 2H), 1.22-1.09 (m, 8H), 0.69 (t, 3H, J = 7.3 Hz).
365		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.84 (br s, 1H), 8.83 (s, 1H), 7.46-7.38 (m, 2H), 7.23-7.15 (m, 2H), 4.94-4.71 (m, 2H), 4.47 (s, 2H), 3.85-3.45 (m, 5H), 1.21-1.12 (m, 6H), 1.02 (d, 3H, J = 6.0 Hz), 0.96 (d, 3H, J = 6.3 Hz).
366			^{1}H-NMR (DMSO-d_6) δ: 12.77 (s, 1H), 8.80 (s, 1H), 7.45-7.38 (m, 2H), 7.23-7.14 (m, 2H), 4.91-4.83 (m, 1H), 4.83-4.73 (m, 2H), 4.47 (s, 2H), 3.86 (dd, 1H, J = 14.1, 3.5 Hz), 3.76-3.67 (m, 1H), 3.54-3.43 (m, 1H), 1.96-1.71 (m, 2H), 1.19 (d, 3H, J = 7.0 Hz), 1.16 (d, 3H, J = 6.7 Hz).
367		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.42 (br s, 1H), 8.84 (s, 1H), 7.45-7.37 (m, 2H), 7.23-7.14 (m, 2H), 4.69-4.63 (m, 1H), 4.53-4.44 (m, 3H), 4.35 (dd, 1H, J = 13.3, 4.0 Hz), 4.18-4.11 (m, 1H), 3.55 (dd, 1H, J = 10.5, 3.6 Hz), 3.48-3.39 (m, 2H), 1.30 (d, 3H, J = 6.9 Hz), 1.28 (d, 3H, J = 6.9 Hz), 0.95-0.90 (m, 6H).

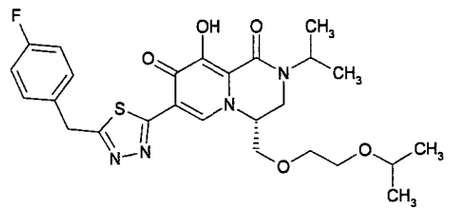
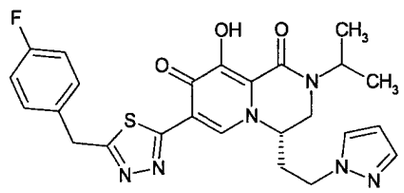
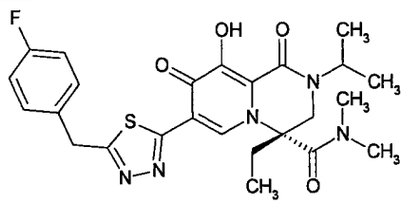
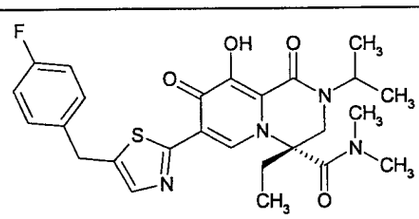
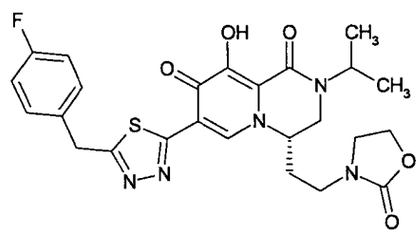
[0516]

[Table 1-100]

No.	structural formula	salt	^{1}H-NMR
368		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.78 (s, 1H), 7.44-7.40 (m, 2H), 7.22-7.16 (m, 2H), 4.74-4.70 (m, 1H), 4.74 (quint, 1H, J = 7.1 Hz), 4.47 (s, 2H), 3.91-3.82 (m, 2H), 3.05 (s, 3H), 1.20 (d, 3H, J = 7.1 Hz), 1.19 (s, 3H), 1.18 (d, 3H, J = 7.1 Hz), 1.10 (s, 3H).
369		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (s, 1H), 8.81 (s, 1H), 7.44-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.95 (s, 1H), 4.80-4.73 (m, 1H), 4.47 (s, 2H), 3.85 (dd, 1H, J = 13.7, 4.0 Hz), 3.75 (d, 1H, J = 13.7 Hz), 3.67 (dd, 1H, J = 10.3, 5.4 Hz), 3.58 (dd, 1H, J = 10.3, 7.7 Hz), 3.45 (dt, 1H, J = 11.4, 4.6 Hz), 3.34 (dt, 1H, J = 11.4, 4.8 Hz), 3.20-3.13 (m, 2H), 3.00 (s, 3H), 1.64-1.58 (m, 2H), 1.16 (dd, 6H, J = 6.9, 2.4 Hz).
370		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.78 (br s, 1H), 8.72 (s, 1H), 7.46-7.38 (m, 2H), 7.24-7.15 (m, 2H), 4.91-4.81 (m, 1H), 4.84-4.72 (m, 1H), 4.47 (s, 2H), 3.89-3.65 (m, 2H), 3.45-3.35 (m, 1H), 3.20-3.07 (m, 1H), 3.18 (s, 3H), 2.07-1.93 (m, 1H), 1.93-1.80 (m, 1H), 1.18 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
371		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (br s, 1H), 8.75 (s, 1H), 7.47-7.37 (m, 2H), 7.24-7.15 (m, 2H), 4.91-4.73 (m, 2H), 4.47 (s, 2H), 3.90-3.63 (m, 2H), 3.58-3.01 (m, 4H), 2.11-1.79 (m, 2H), 1.19 (d, 3H, J = 7.2 Hz), 1.16 (d, 3H, J = 7.2 Hz), 1.03 (t, 3H, J = 7.2 Hz).
372		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.81 (br s, 1H), 8.80 (s, 1H), 7.44-7.36 (m, 2H), 7.23-7.14 (m, 2H), 4.93-4.84 (m, 1H), 4.47 (s, 2H), 4.04 (dd, 1H, J = 13.7, 4.0 Hz), 3.69 (dd, 1H, J = 10.5, 5.6 Hz), 3.66-3.59 (m, 2H), 3.53-3.32 (m, 5H), 2.93-2.85 (m, 1H), 0.96-0.69 (m, 4H), 0.93 (d, 3H, J = 6.0 Hz), 0.90 (d, 3H, J = 6.0 Hz).

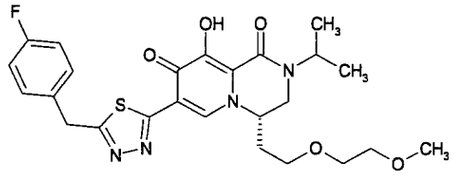
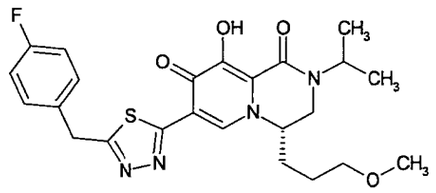
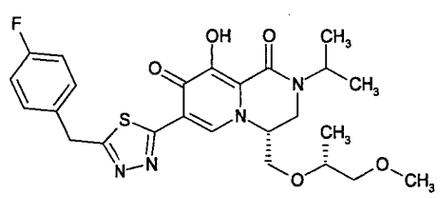
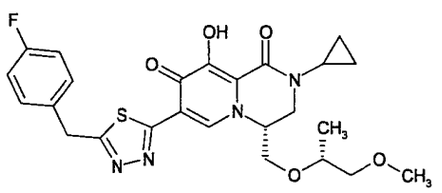
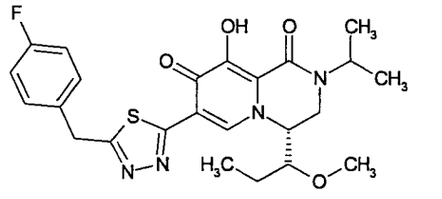
[0517]

[Table 1-101]

No.	structural formula	salt	^{1}H-NMR
373		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.80 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 5.00-4.91 (m, 1H), 4.77 (sep, 1H, J = 6.9 Hz), 4.47 (s, 2H), 3.84 (dd, 1H, J = 13.7, 4.0 Hz), 3.80-3.74 (m, 1H), 3.71 (dd, 1H, J = 10.3, 5.8 Hz), 3.65 (dd, 1H, J = 10.3, 7.9 Hz), 3.54-3.32 (m, 5H), 1.17 (d, 3H, J = 6.9 Hz), 1.16 (d, 3H, J = 6.9 Hz), 0.92 (d, 3H, J = 6.0 Hz), 0.89 (d, 3H, J = 6.0 Hz).
374		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.89 (s, 1H), 7.70 (d, 1H, J = 2.2 Hz), 7.45 (d, 1H, J = 1.8 Hz), 7.44-7.39 (m, 2H), 7.22-7.16 (m, 2H), 6.20 (dd, 1H, J = 2.2, 1.8 Hz), 4.86-4.82 (m, 1H), 4.78 (quint, 1H, J = 7.1 Hz), 4.47 (s, 2H), 4.26-4.14 (m, 2H), 3.84 (dd, 1H, J = 13.6, 3.6 Hz), 3.68 (dd, 1H, J = 13.6, 0.9 Hz), 2.27-2.20 (m, 2H), 1.18 (d, 3H, J = 7.1 Hz), 1.14 (d, 3H, J = 7.1 Hz).
375		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.19 (br s, 1H), 8.41 (s, 1H), 7.46-7.38 (m, 2H), 7.23-7.14 (m, 2H), 4.80-4.68 (m, 1H), 4.47 (s, 2H), 4.08 (d, 1H, J = 14.1 Hz), 3.81 (d, 1H, J = 14.1 Hz), 2.93 (s, 6H), 2.61-2.11 (m, 2H), 1.19 (d, 3H, J = 7.0 Hz), 1.16 (d, 3H, J = 7.0 Hz), 0.91 (t, 3H, J = 7.2 Hz).
376		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.09 (br s, 1H), 8.30 (s, 1H), 7.70 (s, 1H), 7.38-7.28 (m, 2H), 7.19-7.10 (m, 2H), 4.80-4.69 (m, 1H), 4.20 (s, 2H), 4.06 (d, 1H, J = 14.1 Hz), 3.78 (d, 1H, J = 14.1 Hz), 2.91 (s, 6H), 2.47-2.07 (m, 2H), 1.22-1.12 (m, 6H), 0.87 (t, 3H, J = 7.2 Hz).
377		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.78 (br s, 1H), 8.96 (s, 1H), 7.43-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.87-4.80 (m, 1H), 4.80 (quint, 1H, J = 6.6 Hz), 4.47 (s, 2H), 4.23 (t, 2H, J = 7.9 Hz), 3.87-3.82 (m, 1H), 3.76-3.73 (m, 1H), 3.57-3.46 (m, 2H), 3.33-3.25 (m, 1H), 3.19-3.11 (m, 1H), 1.95 (dt, 2H, J = 7.1, 7.9 Hz), 1.22 (d, 3H, J = 6.6 Hz), 1.16 (d, 3H, J = 6.6 Hz).

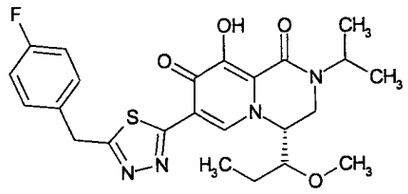
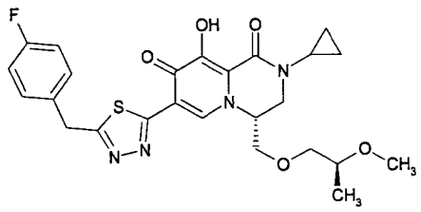
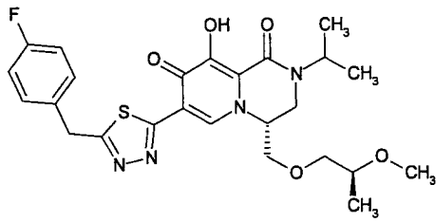
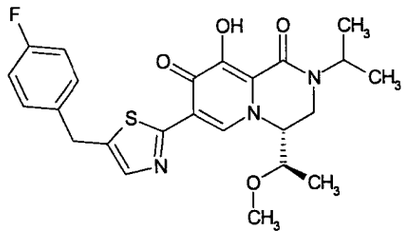
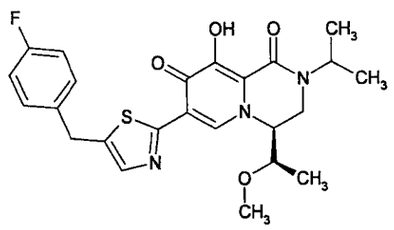
[0518]

[Table 1-102]

No.	structural formula	salt	^{1}H-NMR
378		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.75 (br s, 1H), 8.75 (s, 1H), 7.44-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.88-4.83 (m, 1H), 4.78 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 3.85 (dd, 1H, J = 13.6, 3.6 Hz), 3.73 (dd, 1H, J = 13.6, 0.9 Hz), 3.53-3.48 (m, 1H), 3.45-3.31 (m, 4H), 3.29-3.18 (m, 1H), 3.15 (s, 3H), 2.04-1.96 (m, 1H), 1.91-1.83 (m, 1H), 1.19 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
379		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.78 (br s, 1H), 8.91 (s, 1H), 7.44-7.39 (m, 2H), 7.22-7.16 (m, 2H), 4.83-4.81 (m, 1H), 4.79 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 3.83 (dd, 1H, J = 13.8, 3.6 Hz), 3.72 (dd, 1H, J = 13.8, 1.5 Hz), 3.35-3.22 (m, 2H), 3.18 (s, 3H), 1.81-1.71 (m, 1H), 1.70-1.58 (m, 2H), 1.37-1.33 (m, 1H), 1.18 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
380		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.85 (br s, 1H), 8.83 (s, 1H), 7.46-7.39 (m, 2H), 7.23-7.15 (m, 2H), 4.92-4.83 (br m, 1H), 4.81-4.70 (m, 1H), 4.47 (s, 2H), 3.85-3.62 (m, 4H), 3.59-3.48 (m, 1H), 3.26-3.18 (m, 2H), 3.17 (s, 3H), 1.21-1.12 (m, 6H), 0.91 (d, 3H, J = 6.5 Hz).
381		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.85 (br s, 1H), 8.83 (s, 1H), 7.45-7.37 (m, 2H), 7.23-7.15 (m, 2H), 4.86-4.76 (br m, 1H), 4.47 (s, 2H), 4.02 (dd, 1H, J = 13.4, 4.2 Hz), 3.77-3.58 (m, 3H), 3.57-3.48 (m, 1H), 3.26-3.19 (m, 2H), 3.18 (s, 3H), 2.93-2.84 (m, 1H), 0.92 (d, 3H, J = 6.3 Hz), 0.91-0.70 (m, 4H).
382		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (s, 1H), 8.71 (s, 1H), 7.44-7.42 (m, 2H), 7.21-7.17 (m, 2H), 4.78 (quint, 1H, J = 6.9 Hz), 4.70 (dd, 1H, J = 9.0, 3.7 Hz), 4.47 (s, 2H), 3.87 (dd, 1H, J = 14.5, 3.7 Hz), 3.74 (d, 1H, J = 14.5 Hz), 3.32 (ddd, 1H, J = 9.0, 3.6, 6.0 Hz), 2.96 (s, 3H), 1.79-1.70 (m, 1H), 1.54-1.43 (m, 1H), 1.19 (dd, 6H, J = 10.9, 6.9 Hz), 0.94 (t, 3H, J = 7.5 Hz).

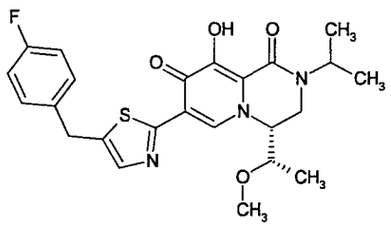
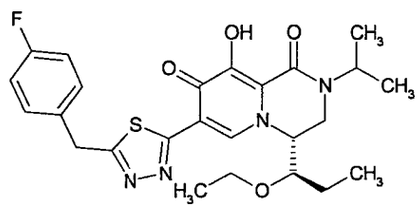
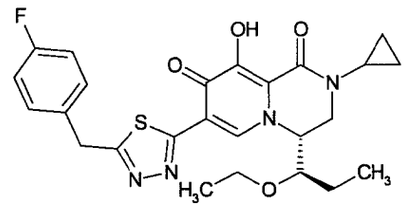
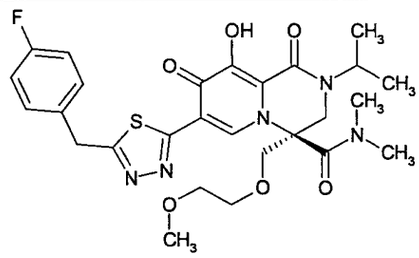
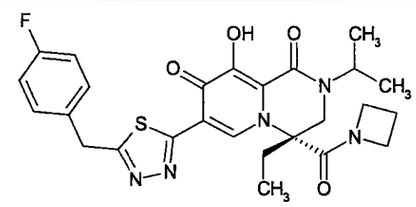
[0519]

[Table 1-103]

No.	structural formula	salt	^{1}H-NMR
383		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.88 (s, 1H), 7.44-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.86-4.82 (m, 1H), 4.77 (quint, 1H, J = 6.9 Hz), 4.47 (s, 2H), 3.83-3.78 (m, 2H), 3.47-3.42 (m, 1H), 3.18 (s, 3H), 1.53-1.47 (m, 1H), 1.33-1.25 (m, 1H), 1.19 (d, 3H, J = 6.9 Hz), 1.17 (d, 3H, J = 6.9 Hz), 0.87 (t, 3H, J = 7.5 Hz).
384		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.82 (br s, 1H), 8.81 (s, 1H), 7.46-7.36 (m, 2H), 7.23-7.15 (m, 2H), 4.93-4.86 (m, 1H), 4.47 (s, 2H), 4.04 (dd, 1H, J = 13.2, 4.2 Hz), 3.75-3.57 (m, 3H), 3.39-3.25 (m, 3H), 3.10 (s, 3H), 2.92-2.87 (m, 1H), 0.93 (d, 3H, J = 5.8 Hz), 0.91-0.67 (m, 4H).
385		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.84 (br s, 1H), 8.82 (s, 1H), 7.45-7.38 (m, 2H), 7.23-7.15 (m, 2H), 5.00-4.92 (br m, 1H), 4.83-4.72 (m, 1H), 4.47 (s, 2H), 3.89-3.59 (m, 4H), 3.41-3.24 (m, 3H), 3.09 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.15 (d, 3H, J = 6.7 Hz), 0.93 (d, 3H, J = 6.3 Hz).
386		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.69 (br s, 1H), 8.56 (s, 1H), 7.66 (s, 1H), 7.39-7.30 (m, 2H), 7.19-7.11 (m, 2H), 4.83-4.71 (m, 1H), 4.63-4.54 (m, 1H), 4.20 (s, 2H), 3.86 (dd, 1H, J = 14.1, 4.2 Hz), 3.78-3.70 (m, 1H), 3.55-3.45 (m, 1H), 3.02 (s, 3H), 1.23-1.14 (m, 9H).
387		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.68 (br s, 1H), 8.74 (s, 1H), 7.68 (s, 1H), 7.37-7.30 (m, 2H), 7.19-7.11 (m, 2H), 4.84-4.73 (m, 1H), 4.69-4.63 (m, 1H), 4.20 (s, 2H), 3.89-3.81 (m, 1H), 3.76 (dd, 1H, J = 13.7, 4.0 Hz), 3.60-3.52 (m, 1H), 3.22 (s, 3H), 1.21-1.15 (m, 6H), 1.00 (d, 3H, J = 6.0 Hz).

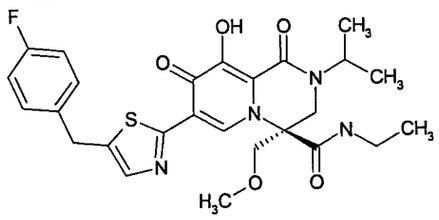
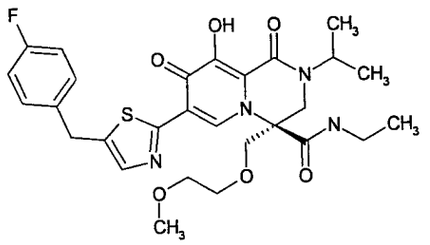
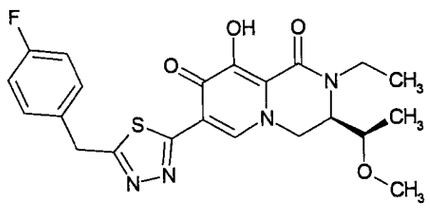
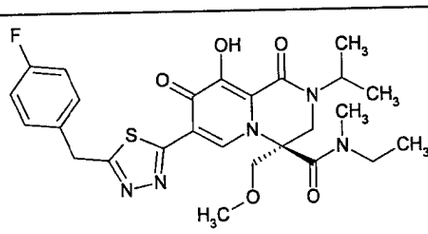
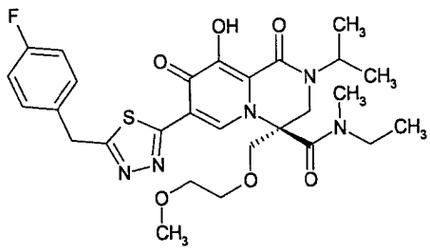
[0520]

[Table 1-104]

No.	structural formula	salt	^{1}H-NMR
388		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.74 (s, 1H), 7.68 (s, 1H), 7.37-7.31 (m, 2H), 7.18-7.11 (m, 2H), 4.84-4.73 (m, 1H), 4.69-4.63 (m, 1H), 4.20 (s, 2H), 3.89-3.81 (m, 1H), 3.76 (dd, 1H, J = 13.7, 4.0 Hz), 3.60-3.51 (m, 1H), 3.22 (s, 3H), 1.21-1.14 (m, 6H), 1.00 (d, 3H, J = 6.0 Hz).
389		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.81 (s, 1H), 8.73 (s, 1H), 7.45-7.42 (m, 2H), 7.21-7.18 (m, 2H), 4.82-4.75 (m, 1H), 4.65 (dd, 1H, J = 9.1, 2.6 Hz), 4.47 (s, 3H), 3.87 (dd, 1H, J = 13.3, 3.8 Hz), 3.74 (d, 1H, J = 13.3 Hz), 3.39-3.27 (m, 2H), 2.77-2.73 (m, 1H), 1.79-1.70 (m, 1H), 1.51-1.43 (m, 1H), 1.20 (d, 3H, J = 6.9 Hz), 1.17 (d, 3H, J = 6.9 Hz), 0.96 (t, 3H, J = 7.5 Hz), 0.74 (t, 3H, J = 6.9 Hz).
390		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.72 (s, 1H), 7.44-7.42 (m, 2H), 7.21-7.17 (m, 2H), 4.62 (d, 1H, J = 5.6 Hz), 4.47 (s, 2H), 4.05 (dd, 1H, J = 13.9, 3.8 Hz), 3.57 (d, 1H, J = 13.3 Hz), 3.47-3.45 (m, 1H), 3.34 (dd, 1H, J = 9.3, 6.9 Hz), 2.94 (dd, 1H, J = 7.7, 3.6 Hz), 2.86 (dd, 1H, J = 9.3, 7.3 Hz), 1.55-1.38 (m, 2H), 0.94 (t, 3H, J = 7.0 Hz), 0.78 (t, 3H, J = 6.5 Hz), 0.42-0.36 (m, 1H), 0.34-0.27 (m, 2H), 0.24-0.20 (m, 1H).
391		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.90 (s, 1H), 8.86 (s, 1H), 7.47-7.37 (m, 2H), 7.23-7.15 (m, 2H), 4.81-4.65 (m, 1H), 4.47 (s, 2H), 4.41 (d, 1H, J = 12.1 Hz), 4.25 (d, 1H, J = 12.1 Hz), 4.06 (d, 1H, J = 14.1 Hz), 3.81 (d, 1H, J = 14.1 Hz), 3.75-3.63 (m, 2H), 3.62-3.36 (m, 2H), 3.21 (s, 3H), 3.11-2.73 (m, 6H), 1.16 (d, 3H, J = 6.8 Hz), 1.10 (d, 3H, J = 6.8 Hz).
392		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.04 (s, 1H), 8.69 (s, 1H), 7.46-7.38 (m, 2H), 7.23-7.14 (m, 2H), 4.76-4.62 (m, 1H), 4.48 (s, 2H), 4.18-4.04 (m, 1H), 3.98 (d, 1H, J = 13.5 Hz), 3.94-3.82 (m, 2H), 3.78 (d, 1H, J = 13.5 Hz), 3.70-3.57 (m, 1H), 2.50-2.22 (m, 2H), 2.15-2.00 (m, 2H), 1.16 (t, 6H, J = 6.8 Hz), 1.03 (t, 3H, J = 7.5 Hz).

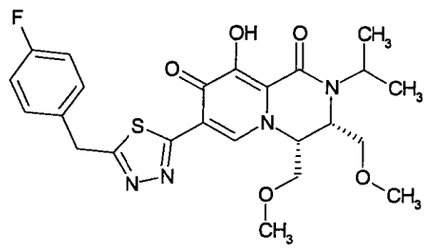
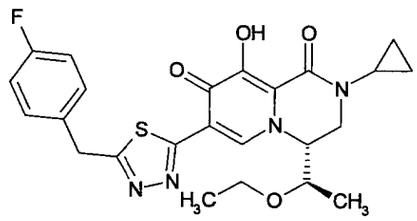
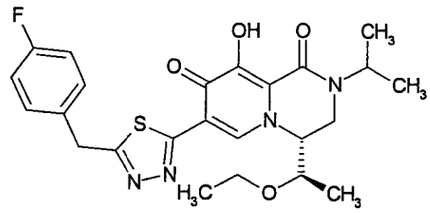
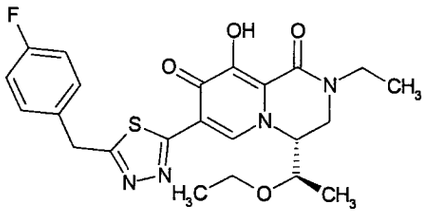
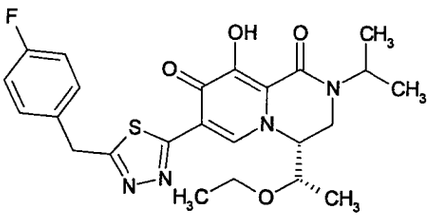
[0521]

[Table 1-105]

No.	structural formula	salt	^{1}H-NMR
393		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.80 (s, 1H), 8.16 (t, 1H, J = 5.5 Hz), 7.67 (s, 1H), 7.38-7.28 (m, 2H), 7.19-7.10 (m, 2H), 4.76-4.63 (m, 1H), 4.20 (s, 2H), 4.17 (d, 1H, J = 11.9 Hz), 4.12 (d, 1H, J = 11.9 Hz), 4.03 (d, 1H, J = 13.9 Hz), 3.76 (d, 1H, J = 13.9 Hz), 3.40 (s, 3H), 3.21-2.92 (m, 2H), 1.13 (d, 3H, J = 6.8 Hz), 1.10 (d, 3H, J = 6.8 Hz), 0.99 (t, 3H, J = 7.5 Hz).
394		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.88 (s, 1H), 8.17 (t, 1H, J = 5.1 Hz), 7.66 (s, 1H), 7.37-7.29 (m, 2H), 7.19-7.10 (m, 2H), 4.76-4.64 (m, 1H), 4.33-4.16 (m, 2H), 4.20 (s, 2H), 4.04 (d, 1H, J = 13.9 Hz), 3.78 (d, 1H, J = 13.9 Hz), 3.72-3.66 (m, 2H), 3.57-3.50 (m, 2H), 3.25 (s, 3H), 3.20-2.96 (m, 2H), 1.14 (d, 3H, J = 6.8 Hz), 1.10 (d, 3H, J = 6.8 Hz), 1.04 (t, 3H, J = 7.3 Hz).
395		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.50 (br s, 1H), 8.95 (s, 1H), 7.44-7.36 (m, 2H), 7.22-7.15 (m, 2H), 4.69 (dd, 1H, J = 14.0, 1.5 Hz), 4.47 (s, 2H), 4.39 (dd, 1H, J = 14.0, 4.2 Hz), 4.04-3.98 (m, 1H), 3.97-3.92 (m, 1H), 3.51-3.43 (m, 1H), 3.26-3.18 (m, 1H), 3.18 (s, 3H), 1.19 (t, 3H, J = 7.2 Hz), 1.10 (d, 3H, J = 6.2 Hz).
396		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.92 (s, 1H), 8.77 (s, 1H), 7.47-7.37 (m, 2H), 7.23-7.14 (m, 2H), 4.79-4.66 (m, 1H), 4.47 (s, 2H), 4.28 (d, 1H, J = 11.9 Hz), 4.12 (d, 1H, J = 11.9 Hz), 4.06 (d, 1H, J = 14.3 Hz), 3.82 (d, 1H, J = 14.3 Hz), 3.47-3.29 (m, 5H), 3.05-2.78 (m, 3H), 1.16 (d, 3H, J = 7.1 Hz), 1.12 (d, 3H, J = 7.1 Hz), 1.08-0.97 (m, 3H).
397		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.93 (s, 1H), 8.85 (s, 1H), 7.48-7.34 (m, 2H), 7.24-7.13 (m, 2H), 4.77-4.65 (m, 1H), 4.47 (s, 2H), 4.38 (d, 1H, J = 11.9 Hz), 4.23 (d, 1H, J = 11.9 Hz), 4.06 (d, 1H, J = 14.3 Hz), 3.82 (d, 1H, J = 14.3 Hz), 3.73-3.24 (m, 6H), 3.19 (s, 3H), 3.06-2.84 (m, 3H), 1.16 (d, 3H, J = 6.6 Hz), 1.12 (d, 3H, J = 6.6 Hz), 1.07-0.94 (m, 3H).

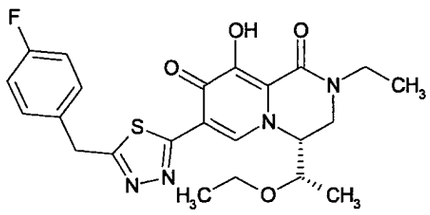
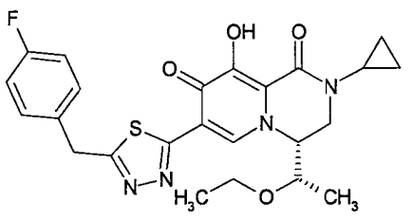
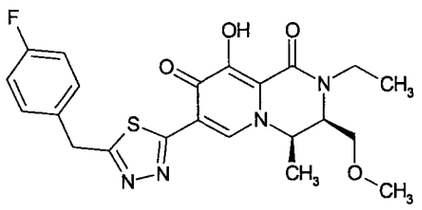
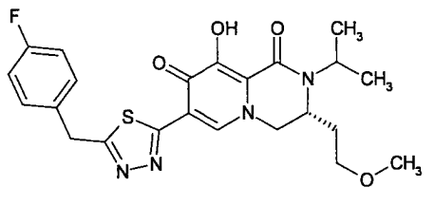
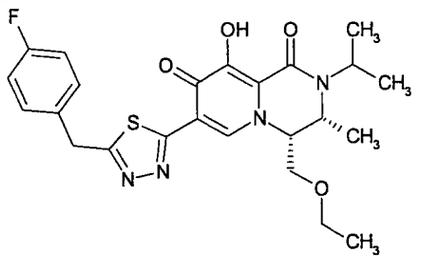
[0522]

[Table 1-106]

No.	structural formula	salt	^{1}H-NMR
398		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.69 (br s, 1H), 8.78 (s, 1H), 7.44-7.36 (m, 2H), 7.22-7.14 (m, 2H), 4.84-4.79 (m, 1H), 4.47 (s, 2H), 4.46-4.37 (m, 1H), 4.22-4.13 (m, 2H), 4.01 (dd, 1H, J = 11.9, 2.2 Hz), 3.49-3.39 (m, 2H), 3.46 (s, 3H), 3.14 (s, 3H), 1.33 (d, 3H, J = 6.9 Hz), 1.30 (d, 3H, J = 6.9 Hz).
399		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.75 (s, 1H), 8.73 (s, 1H), 7.47-7.39 (m, 2H), 7.23-7.15 (m, 2H), 4.60-4.52 (m, 1H), 4.47 (s, 2H), 4.06 (dd, 1H, J = 14.1, 4.0 Hz), 3.65-3.55 (m, 2H), 3.47-3.36 (m, 1H), 3.02-2.88 (m, 2H), 1.16 (d, 3H, J = 6.2 Hz), 0.94-0.82 (m, 3H), 0.79 (t, 3H, J = 7.3 Hz), 0.75-0.64 (m, 1H).
400		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (s, 1H), 8.72 (s, 1H), 7.47-7.39 (m, 2H), 7.24-7.15 (m, 2H), 4.84-4.71 (m, 1H), 4.60 (dd, 1H, J = 8.6, 2.6 Hz), 4.47 (s, 2H), 3.88 (dd, 1H, J = 14.3, 4.0 Hz), 3.75 (d, 1H, J = 13.9 Hz), 3.58-3.53 (m, 1H), 3.46-3.34 (m, 1H), 2.97-2.85 (m, 1H), 1.26-1.14 (m, 9H), 0.75 (t, 3H, J = 6.9 Hz).
401		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.72 (s, 1H), 7.47-7.39 (m, 2H), 7.24-7.15 (m, 2H), 4.60-4.53 (m, 1H), 4.47 (s, 2H), 4.11 (dd, 1H, J = 14.1, 4.2 Hz), 3.75 (d, 1H, J = 13.5 Hz), 3.65-3.37 (m, 4H), 3.00-2.90 (m, 1H), 1.22 (d, 3H, J = 6.2 Hz), 1.16 (t, 3H, J = 7.1 Hz), 0.77 (t, 3H, J = 6.9 Hz).
402		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.90 (s, 1H), 8.32 (s, 1H), 7.44-7.40 (m, 2H), 7.22-7.17 (m, 2H), 4.81-4.74 (m, 1H), 4.71 (t, 1H, J = 4.8 Hz), 4.47 (s, 2H), 3.87 (d, 1H, J = 12.5 Hz), 3.78 (dd, 1H, J = 13.9, 4.2 Hz), 3.71-3.65 (m, 1H), 3.57-3.50 (m, 1H), 3.17-3.10 (m, 1H), 1.19 (t, 6H, J = 7.0 Hz), 1.06 (d, 3H, J = 6.0 Hz), 1.02 (t, 3H, J = 6.9 Hz).

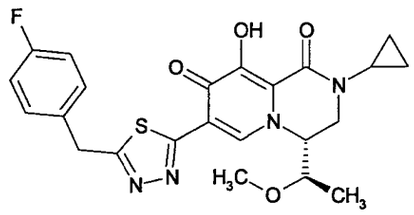
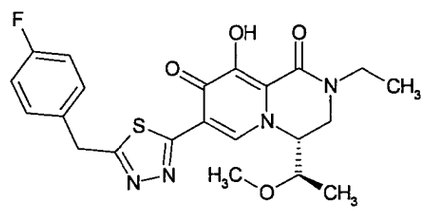
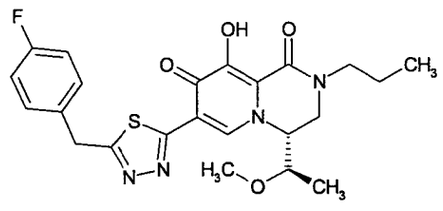
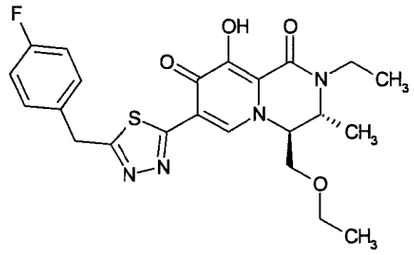
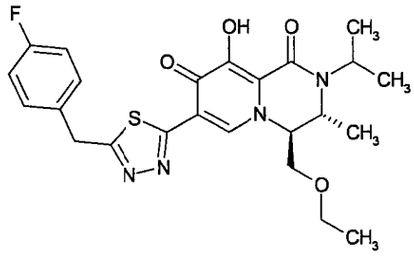
[0523]

[Table 1-107]

No.	structural formula	salt	^{1}H-NMR
403		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (s, 1H), 8.91 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.69 (t, 1H, J = 4.6 Hz), 4.47 (s, 2H), 4.02 (dd, 1H, J = 14.1, 4.4 Hz), 3.84 (d, 1H, J = 13.7 Hz), 3.73-3.67 (m, 1H), 3.65-3.58 (m, 1H), 3.56-3.39 (m, 2H), 3.21-3.15 (m, 1H), 1.16 (t, 3H, J = 7.1 Hz), 1.07 (d, 3H, J = 6.0 Hz), 1.01 (t, 3H, J = 6.9 Hz).
404		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (s, 1H), 8.90 (s, 1H), 7.43-7.39 (m, 2H), 7.22-7.16 (m, 2H), 4.66 (t, 1H, J = 4.4 Hz), 4.47 (s, 2H), 3.98 (dd, 1H, J = 13.9, 4.2 Hz), 3.74-3.65 (m, 2H), 3.56-3.48 (m, 1H), 3.20-3.14 (m, 1H), 2.92-2.87 (m, 1H), 1.04 (d, 3H, J = 7.0 Hz), 1.02 (t, 3H, J = 7.2 Hz), 0.94-0.89 (m, 1H), 0.87-0.80 (m, 2H), 0.75-0.70 (m, 1H).
405		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (br s, 1H), 8.62 (s, 1H), 7.42-7.38 (m, 2H), 7.20-7.16 (m, 2H), 4.77-4.71 (m, 1H), 4.47 (s, 2H), 4.14 (q, 1H, J=4.0 Hz), 3.92-3.84 (m, 1H), 3.59 (d, 2H, J=4.4 Hz), 3.33-3.26 (m, 1H), 3.18 (s, 3H), 1.64 (d, 3H, J=6.5 Hz), 1.21 (t, 3H, J=7.1 Hz).
406		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.44 (br s, 1H), 8.89 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.66-4.60 (m, 1H), 4.56-4.45 (m, 3H), 4.34-4.27 (m, 1H), 4.10-4.04 (m, 1H), 3.50-3.36 (m, 2H), 3.24 (s, 3H), 1.89-1.79 (m, 1H), 1.73-1.62 (m, 1H), 1.28 (d, 6H, J = 6.9 Hz).
407		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (br s, 1H), 8.88 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.15 (m, 2H), 4.71-4.66 (m, 1H), 4.62-4.52 (m, 1H), 4.47 (s, 2H), 4.21-4.07 (m, 2H), 3.99 (dd, 1H, J = 11.7, 2.0 Hz), 3.71-3.62 (m, 2H), 1.32-1.22 (m, 9H), 1.05 (d, 3H, J = 6.4 Hz).

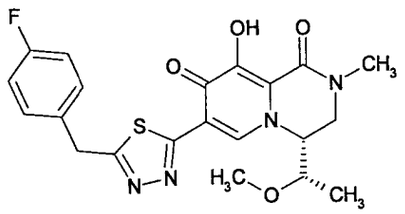
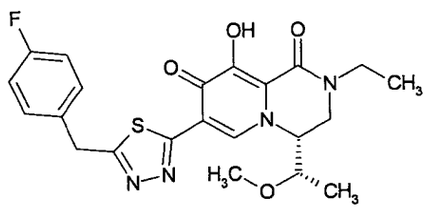
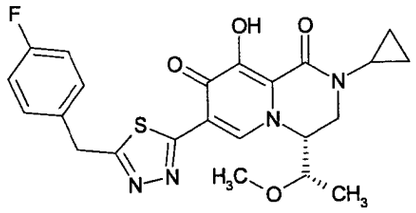
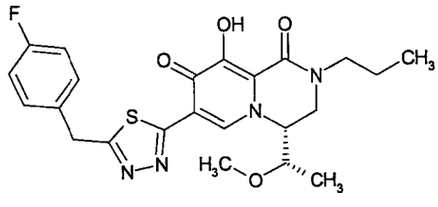
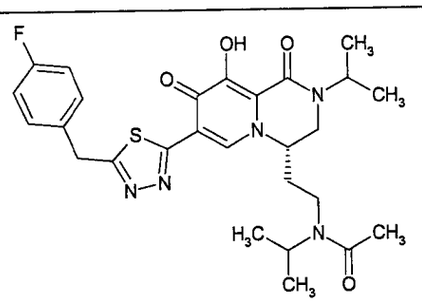
[0524]

[Table 1-108]

No.	structural formula	salt	^{1}H-NMR
408		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.73 (s, 1H), 8.72 (s, 1H), 7.44-7.40 (m, 2H), 7.22-7.16 (m, 2H), 4.64-4.55 (m, 1H), 4.47 (s, 2H), 4.06 (dd, 1H, J = 14.1, 4.2 Hz), 3.66-3.49 (m, 2H), 3.06 (s, 3H), 2.96-2.86 (m, 1H), 1.15 (d, 3H, J = 6.0 Hz), 0.96-0.78 (m, 3H), 0.75-0.63 (m, 1H).
409		HCl	^{1}H-NMR (DMSO-D_6) δ: 12.73 (br s, 1H), 8.71 (s, 1H), 7.47-7.39 (m, 2H), 7.24-7.15 (m, 2H), 4.66-4.56 (m, 1H), 4.47 (s, 2H), 4.11 (dd, 1H, J = 14.1, 4.2 Hz), 3.76 (d, 1H, J = 13.7 Hz), 3.66-3.42 (m, 3H), 3.06 (s, 3H), 1.21 (d, 3H, J = 5.7 Hz), 1.16 (t, 3H, J = 7.3 Hz).
410		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.71 (br s, 1H), 8.71 (s, 1H), 7.47-7.39 (m, 2H), 7.24-7.15 (m, 2H), 4.65-4.57 (m, 1H), 4.47 (s, 2H), 4.10 (dd, 1H, J = 14.1, 4.0 Hz), 3.77 (d, 1H, J = 14.8 Hz), 3.59-3.38 (m, 3H), 3.05 (s, 3H), 1.60 (dt, 2H, J = 7.4, 7.4 Hz), 1.21 (d, 3H, J = 6.2 Hz), 0.90 (t, 3H, J = 7.4 Hz).
411		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.67 (s, 1H), 8.83 (s, 1H), 7.45-7.37 (m, 2H), 7.23-7.14 (m, 2H), 4.81 (t, 1H, J = 6.3 Hz), 4.48 (s, 2H), 4.09-3.99 (m, 1H), 3.97-3.85 (m, 1H), 3.68 (dd, 1H, J = 10.6, 5.7 Hz), 3.55 (dd, 1H, J = 10.6, 7.6 Hz), 3.51-3.30 (m, 2H), 3.19-3.06 (m, 1H), 1.27 (d, 3H, J = 6.6 Hz), 1.17 (t, 3H, J = 6.8 Hz), 1.01 (t, 3H, J = 7.3 Hz).
412		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.68 (br s, 1H), 8.83 (s, 1H), 7.46-7.37 (m, 2H), 7.23-7.15 (m, 2H), 4.85-4.76 (m, 1H), 4.67-4.57 (m, 1H), 4.48 (s, 2H), 4.20-4.10 (m, 1H), 3.64 (dd, 1H, J = 10.5, 5.8 Hz), 3.56-3.32 (m, 3H), 1.31-1.18 (m, 9H), 1.02 (t, 3H, J = 7.1 Hz).

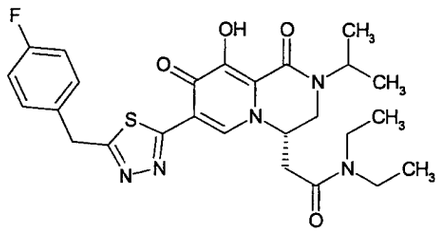
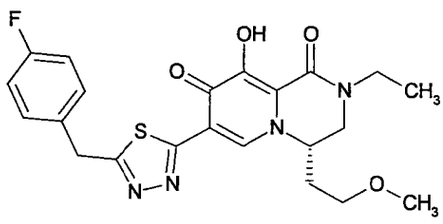
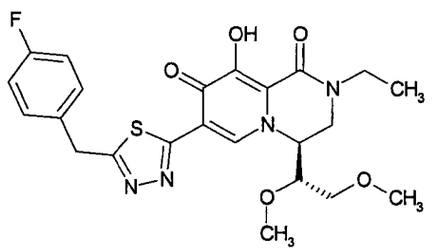
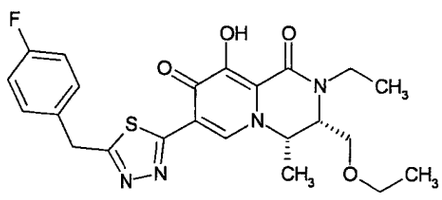
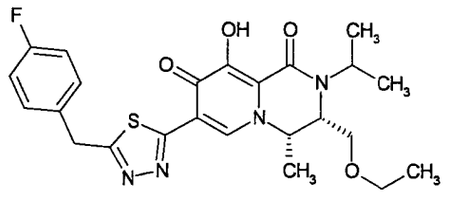
[0525]

[Table 1-109]

No.	structural formula	salt	^{1}H-NMR
413		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.70 (s, 1H), 8.87 (s, 1H), 7.43-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.69 (t, 1H, J = 4.4 Hz), 4.47 (s, 2H), 4.09-4.04 (m, 1H), 3.76 (d, 1H, J = 12.9 Hz), 3.66-3.60 (m, 1H), 3.23 (s, 3H), 3.07 (s, 3H), 1.04 (d, 3H, J = 6.4 Hz).
414		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.76 (s, 1H), 8.90 (s, 1H), 7.44-7.39 (m, 2H), 7.21-7.17 (m, 2H), 4.69 (t, 1H, J = 4.4 Hz), 4.47 (s, 2H), 4.05-4.00 (m, 1H), 3.83 (d, 1H, J = 13.3 Hz), 3.67-3.59 (m, 2H), 3.45-3.39 (m, 1H), 3.23 (s, 3H), 1.16 (t, 3H, J = 7.1 Hz), 1.04 (d, 3H, J = 6.0 Hz).
415		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.75 (s, 1H), 8.89 (s, 1H), 7.43-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.66 (t, 1H, J = 4.6 Hz), 4.47 (s, 2H), 3.98 (dd, 1H, J = 13.7, 4.0 Hz), 3.71 (d, 1H, J = 12.5 Hz), 3.59-3.53 (m, 1H), 3.22 (s, 3H), 2.94-2.88 (m, 1H), 1.02 (d, 3H, J = 6.0 Hz), 0.95-0.89 (m, 1H), 0.85-0.80 (m, 2H), 0.75-0.69 (m, 1H).
416		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.75 (s, 1H), 8.90 (s, 1H), 7.43-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.69 (t, 1H, J = 4.8 Hz), 4.47 (s, 2H), 4.01 (dd, 1H, J = 13.9, 4.2 Hz), 3.83 (d, 1H, J = 12.9 Hz), 3.64-3.58 (m, 1H), 3.55-3.48 (m, 1H), 3.41-3.34 (m, 1H), 3.21 (s, 3H), 1.63-1.58 (m, 2H), 1.05 (d, 3H, J = 6.0 Hz), 0.91 (t, 3H, J = 7.3 Hz).
417		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.86 (s, 1H), 7.44-7.35 (m, 2H), 7.19-7.09 (m, 2H), 4.86-4.68 (m, 2H), 4.45 (s, 2H), 3.90-3.80 (m, 1H), 3.76-3.67 (m, 1H), 3.46-2.59 (m, 3H), 2.14-1.65 (m, 5H), 1.24 (d, 3H, J = 7.1 Hz), 1.19 (d, 3H, J = 7.1 Hz), 1.14-0.98 (m, 6H).

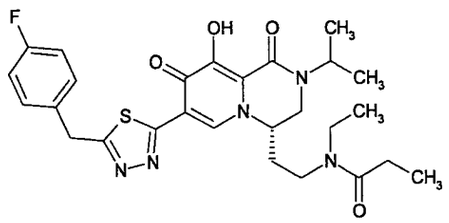
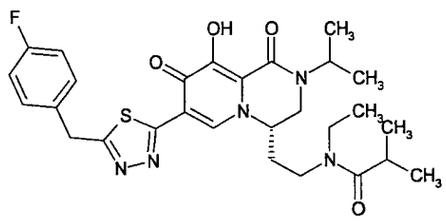
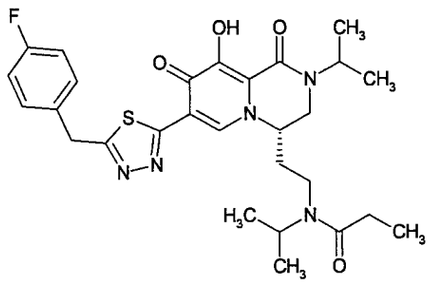
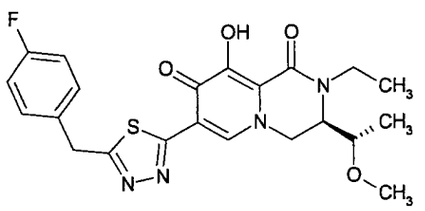
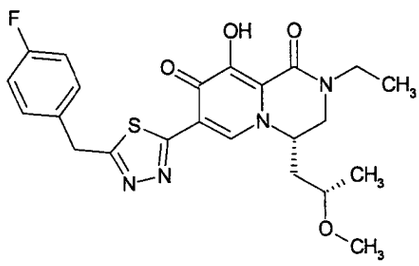
[0526]

[Table 1-110]

No.	structural formula	salt	^{1}H-NMR
418		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.84 (s, 1H), 7.46-7.36 (m, 2H), 7.23-7.14 (m, 2H), 5.21-5.10 (m, 1H), 4.86-4.73 (m, 1H), 4.47 (s, 2H), 3.84 (d, 2H, J = 2.2 Hz), 3.37-3.11 (m, 4H), 2.87 (d, 2H, J = 7.1 Hz), 1.13 (t, 6H, J = 7.3 Hz), 0.99 (t, 3H, J = 7.1 Hz), 0.95 (t, 3H, J = 7.1 Hz).
419		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.73 (s, 1H), 7.47-7.38 (m, 2H), 7.23-7.15 (m, 2H), 4.89-4.76 (m, 1H), 4.47 (s, 2H), 4.20-3.99 (m, 2H), 3.72-3.57 (m, 2H), 3.51-3.32 (m, 2H), 3.18 (s, 3H), 2.15-1.83 (m, 2H), 1.16 (t, 3H, J = 7.3 Hz).
420		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.75 (br s, 1H), 8.64 (s, 1H), 7.46-7.39 (m, 2H), 7.22-7.15 (m, 2H), 4.77-4.71 (m, 1H), 4.47 (s, 2H), 4.11 (dd, 1H, J = 13.7, 4.0 Hz), 3.77-3.71 (m, 1H), 3.64-3.44 (m, 5H), 3.33 (s, 3H), 3.10 (s, 3H), 1.20-1.13 (m, 3H).
421		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (br s, 1H), 8.61 (s, 1H), 7.46-7.34 (m, 2H), 7.24-7.14 (m, 2H), 4.81-4.69 (m, 1H), 4.47 (s, 2H), 4.15-4.08 (m, 1H), 3.90 (td, 1H, J = 13.9, 7.0 Hz), 3.64 (d, 2H, J = 4.2 Hz), 3.38-3.21 (m, 3H), 1.65 (d, 3H, J = 7.0 Hz), 1.22 (t, 3H, J = 7.3 Hz), 0.89 (t, 3H, J = 6.8 Hz).
422		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.72 (br s, 1H), 8.55 (s, 1H), 7.45-7.36 (m, 2H), 7.23-7.14 (m, 2H), 4.72-4.61 (m, 1H), 4.49-4.38 (m, 1H), 4.47 (s, 2H), 4.09-4.02 (m, 1H), 3.61 (dd, 1H, J = 11.1, 3.0 Hz), 3.54 (dd, 1H, J = 11.1, 3.9 Hz), 3.27 (q, 2H, J = 7.0 Hz), 1.75 (d, 3H, J = 6.6 Hz), 1.32 (t, 6H, J = 6.8 Hz), 0.82 (t, 3H, J = 7.0 Hz).

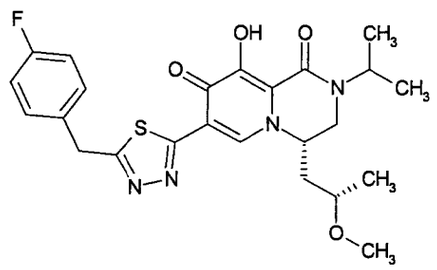
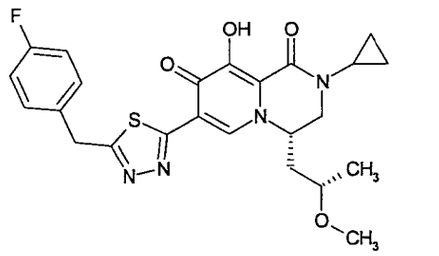
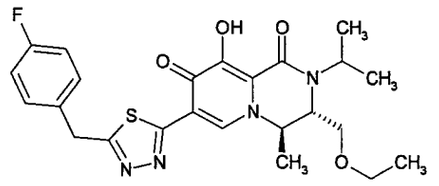
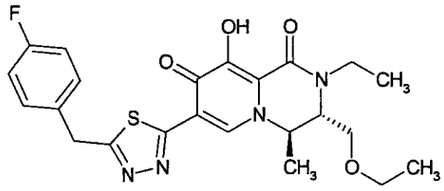
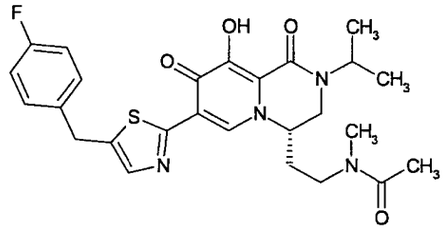
[0527]

[Table 1-111]

No.	structural formula	salt	^{1}H-NMR
423		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.83 (s, 1H), 7.44-7.35 (m, 2H), 7.18-7.09 (m, 2H), 4.84-4.66 (m, 2H), 4.45 (s, 2H), 3.90-3.79 (m, 1H), 3.77-3.64 (m, 1H), 3.48-2.60 (m, 4H), 2.33-2.17 (m, 2H), 2.08-1.77 (m, 2H), 1.24 (d, 3H, J = 6.4 Hz), 1.19 (d, 3H, J = 6.6 Hz), 1.12-1.00 (m, 3H), 0.97 (t, 3H, J = 7.7 Hz).
424		HCl	^{1}H-NMR (DMSO-d_6) δ: 9.02 (s, 0.25H), 8.94 (s, 0,75H), 7.46-7.36 (m, 2H), 7.23-7.14 (m, 2H), 4.95-4.66 (br m, 2H), 4.47 (s, 2H), 3.92-3.67 (m, 2H), 3.53-2.98 (br m, 4H), 2.87-2.53 (br m, 1H), 2.14-1.63 (br m, 2H), 1.29-0.86 (br m, 15H).
425		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.86 (s, 1H), 7.44-7.35 (m, 2H), 7.19-7.08 (m, 2H), 4.85-4.69 (m, 2H), 4.45 (s, 2H), 4.22-3.98 (m, 2H), 3.90-3.80 (m, 1H), 3.78-3.68 (m, 1H), 3.13-3.00 (m, 1H), 2.35-2.15 (m, 2H), 2.09-1.93 (m, 1H), 1.87-1.71 (m, 1H), 1.24 (d, 3H, J = 6.6 Hz), 1.19 (d, 3H, J = 6.8 Hz), 1.07 (t, 6H, J = 6.4 Hz), 0.96 (t, 3H, J = 7.3 Hz).
426		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.49 (s, 1H), 8.91 (s, 1H), 7.42-7.39 (m, 2H), 7.20-7.16 (m, 2H), 4.80 (d, 1H, J = 13.3 Hz), 4.47 (s, 2H), 4.36 (dd, 1H, J = 13.7, 4.8 Hz), 3.96-3.89 (m, 2H), 3.65-3.60 (m, 1H), 3.28-3.20 (m, 1H), 3.08 (s, 3H), 1.21 (t, 3H, J = 7.1 Hz), 1.16 (d, 3H, J = 6.4 Hz).
427		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.65 (s, 1H), 7.44-7.39 (m, 2H), 7.22-7.16 (m, 2H), 4.88-4.84 (m, 1H), 4.46 (s, 2H), 4.08 (dd, 1H, J = 13.5, 3.8 Hz), 3.65-3.62 (m, 1H), 3.62 (dq, 1H, J = 13.7, 7.3 Hz), 3.45 (dq, 1H, J = 13.7, 7.3 Hz), 3.21 (s, 3H), 3.02-2.97 (m, 1H), 1.93-1.78 (m, 2H), 1.16 (t, 3H, J = 7.3 Hz), 1.04 (d, 3H, J = 6.0 Hz).

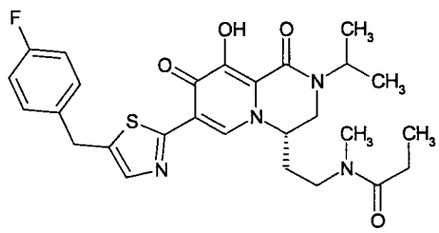
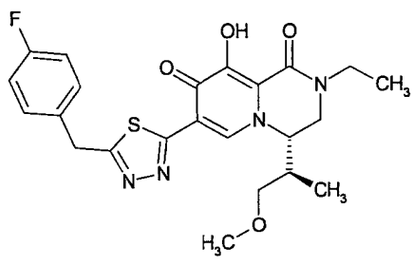
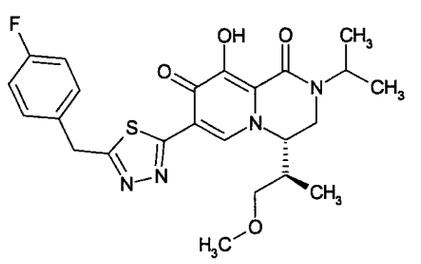
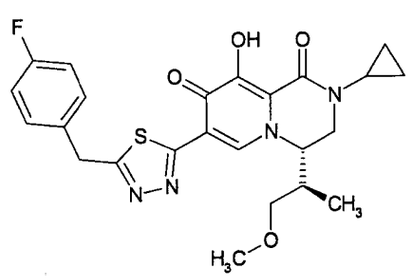
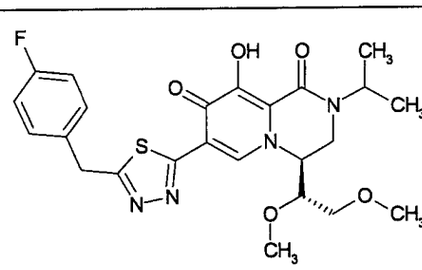
[0528]

[Table 1-112]

No.	structural formula	salt	^{1}H-NMR
428		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (s, 1H), 8.64 (s, 1H), 7.44-7.40 (m, 2H), 7.21-7.17 (m, 2H), 4.91-4.87 (m, 1H), 4.78 (sep, 1H, J = 6.8 Hz), 4.46 (s, 2H), 3.84 (dd, 1H, J = 13.5, 3.6 Hz), 3.68 (dd, 1H, J = 13.5, 1.3 Hz), 3.22 (s, 3H), 2.99-2.95 (m, 1H), 1.86 (ddd, 1H, J = 14.6, 9.9, 3.1 Hz), 1.77 (ddd, 1H, J = 14.6, 10.4, 4.9 Hz), 1.18 (d, 3H, J = 6.8 Hz), 1.15 (d, 3H, J = 6.8 Hz), 1.04 (d, 3H, J = 6.0 Hz).
429		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (br s, 1H), 8.65 (s, 1H), 7.44-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.85-4.80 (m, 1H), 4.46 (s, 2H), 4.02 (dd, 1H, J = 13.2, 3.7 Hz), 3.54 (dd, 1H, J = 13.2, 0.9 Hz), 3.21 (s, 3H), 3.03-2.96 (m, 1H), 2.97-2.91 (m, 1H), 1.85-1.75 (m, 2H), 1.03 (d, 3H, J = 6.0 Hz), 0.95-0.72 (m, 4H).
430		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.48 (br s, 1H), 8.95 (s, 1H), 7.45-7.37 (m, 2H), 7.23-7.14 (m, 2H), 5.01-4.90 (m, 1H), 4.56 (sep, 1H, J = 6.8 Hz), 4.48 (s, 2H), 4.08-4.01 (m, 1H), 3.55 (dd, 1H, J = 10.5, 3.9 Hz), 3.45-3.31 (m, 3H), 1.40 (d, 3H, J = 6.6 Hz), 1.29 (d, 3H, J = 6.8 Hz), 1.28 (d, 3H, J = 6.8 Hz), 0.98 (t, 3H, J = 6.9 Hz).
431		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.50 (br s, 1H), 8.93 (s, 1H), 7.45-7.36 (m, 2H), 7.23-7.14 (m, 2H), 4.92 (q, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.04-3.96 (m, 2H), 3.59-3.47 (m, 2H), 3.44-3.31 (m, 2H), 3.22-3.09 (m, 1H), 1.42 (d, 3H, J = 6.7 Hz), 1.20 (t, 3H, J = 7.1 Hz), 0.97 (t, 3H, J = 6.9 Hz).
432		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.80-8.74 (m, 1H), 7.68 (s, 1H), 7.38-7.29 (m, 2H), 7.20-7.10 (m, 2H), 4.97-4.55 (m, 2H), 4.20 (s, 2H), 3.92-3.60 (m, 2H), 3.60-3.02 (m, 2H), 2.93 (s, 2H), 2.72 (s, 1H), 2.08-1.59 (m, 5H), 1.22 (d, 3H, J = 7.1 Hz), 1.16 (d, 3H, J = 6.4 Hz).

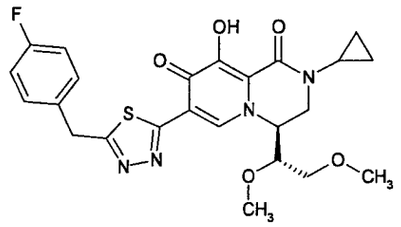
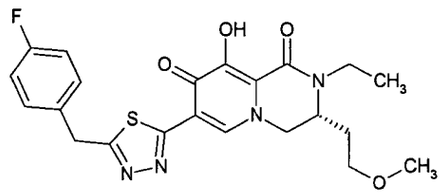
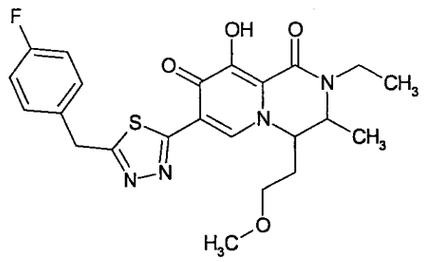
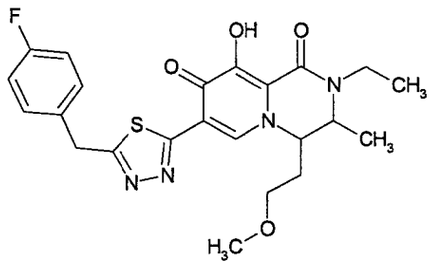
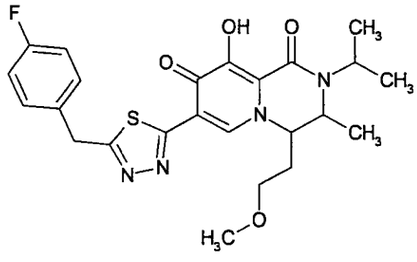
[0529]

[Table 1-113]

No.	structural formula	salt	^{1}H-NMR
433		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.66 (s, 1H), 7.61 (s, 1H), 7.36-7.27 (m, 2H), 7.16-7.04 (m, 2H), 4.84-4.56 (m, 2H), 4.19 (s, 2H), 3.88-3.76 (m, 1H), 3.75-3.63 (m, 1H), 3.52-3.14 (m, 2H), 3.03-2.70 (m, 3H), 2.33-2.17 (m, 2H), 2.06-1.76 (m, 2H), 1.24 (d, 3H, J = 6.6 Hz), 1.19 (d, 3H, J = 6.6 Hz), 0.96 (t, 3H, J = 7.5 Hz).
434		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.63 (br s, 1H), 8.73 (s, 1H), 7.44-7.41 (m, 2H), 7.21-7.17 (m, 2H), 4.60-4.55 (m, 1H), 4.47 (s, 2H), 4.05 (dd, 1H, J = 13.9, 3.4 Hz), 3.78 (dd, 1H, J = 13.9, 1.1 Hz), 3.63 (dq, 1H, J = 13.5, 7.1 Hz), 3.48 (dq, 1H, J = 13.5, 7.1 Hz), 3.18 (dd, 1H, J = 9.9, 4.2 Hz), 3.02 (s, 3H), 2.88 (dd, 1H, J = 9.9, 3.4 Hz), 2.11-2.04 (m, 1H), 1.16 (t, 3H, J = 7.1 Hz), 1.07 (d, 3H, J = 6.8 Hz).
435		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.71 (br s, 1H), 8.75 (s, 1H), 7.44-7.41 (m, 2H), 7.22-7.17 (m, 2H), 4.79 (sep, 1H, J = 6.8 Hz), 4.60-4.57 (m, 1H), 4.46 (s, 2H), 3.82 (dd, 1H, J = 14.3, 3.5 Hz), 3.77 (dd, 1H, J = 14.3, 1.3 Hz), 3.16 (dd, 1H, J = 9.9, 4.1 Hz), 2.99 (s, 3H), 2.83 (dd, 1H, J = 9.9, 3.3 Hz), 2.06-2.02 (m, 1H), 1.20 (d, 3H, J = 6.8 Hz), 1.19 (d, 3H, J = 6.8 Hz), 1.08 (d, 3H, J = 6.8 Hz).
436		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.64 (br s, 1H), 8.73 (s, 1H), 7.44-7.40 (m, 2H), 7.21-7.17 (m, 2H), 4.57-4.54 (m, 1H), 4.46 (s, 2H), 4.01 (dd, 1H, J = 13.7, 3.6 Hz), 3.61 (dd, 1H, J = 13.7, 1.2 Hz), 3.17 (dd, 1H, J = 9.9, 4.4 Hz), 3.02 (s, 3H), 2.98-2.92 (m, 1H), 2.88 (dd, 1H, J = 9.9, 3.4 Hz), 2.07-1.99 (m, 1H), 1.03 (d, 3H, J = 6.9 Hz), 0.93-0.81 (m, 3H), 0.72-0.65 (m, 1H).
437		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.65 (s, 1H), 7.46-7.40 (m, 2H), 7.22-7.16 (m, 2H), 4.83-4.71 (m, 2H), 4.47 (s, 2H), 3.93-3.86 (m, 1H), 3.79-3.73 (m, 1H), 3.60-3.47 (m, 3H), 3.33 (s, 3H), 3.08 (s, 3H), 1.22 (d, 3H, J = 6.9 Hz), 1.18 (d, 3H, J = 6.9 Hz).

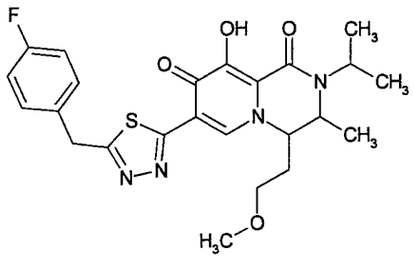
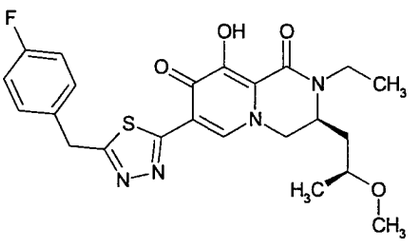
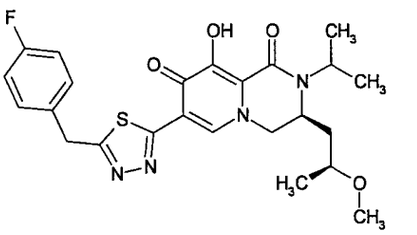
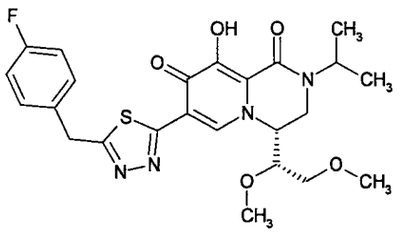
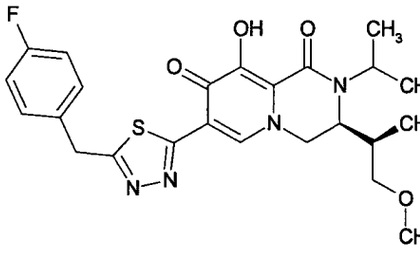
[0530]

[Table 1-114]

No.	structural formula	salt	^{1}H-NMR
438		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.74 (br s, 1H), 8.64 (s, 1H), 7.46-7.39 (m, 2H), 7.22-7.15 (m, 2H), 4.76-4.70 (m, 1H), 4.47 (s, 2H), 4.10-4.02 (m, 1H), 3.67-3.60 (m, 1H), 3.60-3.53 (m, 1H), 3.48 (dd, 1H, J = 10.9, 4.0 Hz), 3.43 (dd, 1H, J = 10.9, 5.2 Hz), 3.32 (s, 3H), 3.10 (s, 3H), 2.96-2.88 (m, 1H), 0.95-0.73 (m, 4H).
439		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.46 (br s, 1H), 8.87 (s, 1H), 7.45-7.36 (m, 2H), 7.23-7.14 (m, 2H), 4.65-4.56 (m, 1H), 4.47 (s, 2H), 4.38 (dd, 1H, J = 13.7, 3.6 Hz), 4.07-3.98 (m, 1H), 3.91 (td, 1H, J = 13.9, 7.1 Hz), 3.48-3.33 (m, 2H), 3.23 (s, 3H), 3.11 (td, 1H, J = 13.9, 7.1 Hz), 1.91-1.79 (m, 1H), 1.79-1.67 (m, 1H), 1.20 (t, 3H, J = 7.1 Hz).
440	 racemate, containing two kinds of diatereomers of Example No. 441	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.63 (s, 1H), 8.76 (s, 1H), 7.44-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.66 (dd, 1H, J = 9.7, 4.4 Hz), 4.47 (s, 2H), 3.97 (dd, 1H, J = 13.9, 6.2 Hz), 3.92-3.86 (m, 1H), 3.41-3.36 (m, 1H), 3.17-3.10 (m, 5H), 2.08-2.01 (m, 1H), 1.87-1.80 (m, 1H), 1.24 (d, 3H, J = 6.4 Hz), 1.19 (t, 3H, J = 7.1 Hz).
441	 racemate, containing two kinds of diatereomers of Example No. 440	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (s, 1H), 8.64 (s, 1H), 7.44-7.40 (m, 2H), 7.22-7.17 (m, 2H), 4.71-4.67 (m, 1H), 4.47 (s, 2H), 4.33-4.27 (m, 1H), 3.76 (td, 1H, J = 14.1, 7.1 Hz), 3.43-3.36 (m, 2H), 3.15 (s, 3H), 3.12-3.05 (m, 1H), 2.09-2.02 (m, 1H), 1.94-1.84 (m, 1H), 1.33 (d, 3H, J = 5.2 Hz), 1.14 (t, 3H, J = 7.1 Hz).
442	 racemate, containing two kinds of diatereomers of Example No. 443	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.65 (s, 1H), 8.75 (s, 1H), 7.43-7.40 (m, 2H), 7.21-7.17 (m, 2H), 4.67-4.58 (m, 2H), 4.47 (s, 2H), 4.10-4.04 (m, 1H), 3.42-3.37 (m, 1H), 3.17 (s, 3H), 3.15-3.09 (m, 1H), 2.05-1.97 (m, 1H), 1.82-1.75 (m, 1H), 1.28-1.23 (m, 9H).

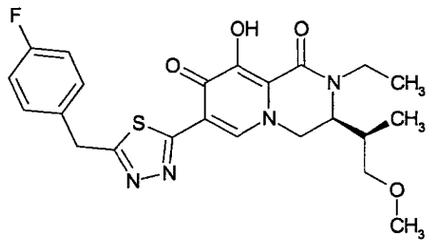
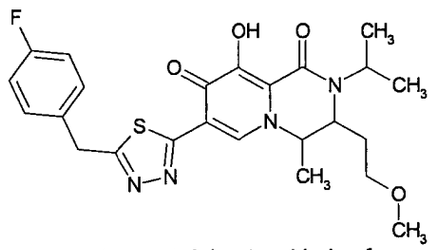
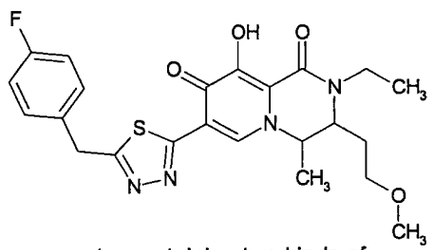
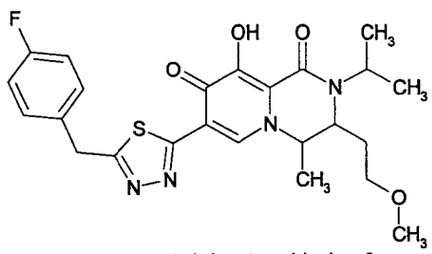
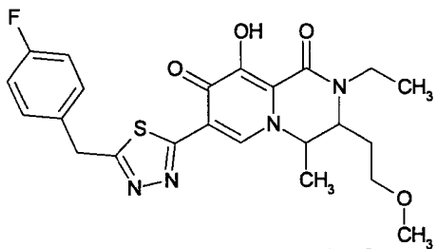
[0531]

[Table 1-115]

No.	structural formula	salt	^{1}H-NMR
443	 racemate, containing two kinds of diatereomers of Example No. 442	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.76 (s, 1H), 8.65 (s, 1H), 7.42-7.39 (m, 2H), 7.20-7.16 (m, 2H), 4.56-4.51 (m, 2H), 4.47 (s, 2H), 4.09-4.03 (m, 1H), 3.63-3.54 (m, 2H), 3.31 (s, 3H), 2.50-2.48 (m, 1H), 2.12-2.06 (m, 1H), 1.30 (d, 3H, J = 7.0 Hz), 1.28 (d, 3H, J = 7.0 Hz), 1.09 (d, 3H, J = 6.0 Hz).
444		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.48 (br s, 1H), 8.80 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.55 (dd, 1H, J = 13.2, 1.5 Hz), 4.47 (s, 2H), 4.38 (dd, 1H, J = 13.2, 3.5 Hz), 4.08-4.04 (m, 1H), 3.98 (dq, 1H, J = 13.5, 7.1 Hz), 3.42-3.37 (m, 1H), 3.20 (s, 3H), 3.06 (dq, 1H, J = 13.5, 7.1 Hz), 1.71-1.59 (m, 2H), 1.20 (t, 3H, J = 7.1 Hz), 1.06 (d, 3H, J = 6.2 Hz).
445		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.81 (s, 1H), 7.44-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.57 (dd, 1H, J = 13.2, 1.3 Hz), 4.47 (s, 2H), 4.45 (sep, 1H, J = 6.8 Hz), 4.31 (dd, 1H, J = 13.2, 3.3 Hz), 4.11-4.06 (m, 1H), 3.50-3.45 (m, 1H), 3.19 (s, 3H), 1.68-1.57 (m, 2H), 1.31 (d, 3H, J = 6.8 Hz), 1.28 (d, 3H, J = 6.8 Hz), 1.08 (d, 3H, J = 6.2 Hz).
446		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (br s, 1H), 8.75 (s, 1H), 7.45-7.39 (m, 2H), 7.22-7.16 (m, 2H), 4.86-4.75 (m, 2H), 4.47 (s, 2H), 3.86-3.80 (m, 1H), 3.76 (dd, 1H, J = 13.3, 3.6 Hz), 3.61 (dd, 1H, J = 11.7, 2.8 Hz), 3.58-3.51 (m, 1H), 3.30 (s, 3H), 3.18 (s, 3H), 2.97 (dd, 1H, J = 11.7, 2.8 Hz), 1.20 (d, 3H, J = 6.9 Hz), 1.17 (d, 3H, J = 6.9 Hz).
447		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.47 (br s, 1H), 8.99 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.73 (d, 1H, J = 13.7 Hz), 4.47 (s, 2H), 4.34 (dd, 1H, J = 13.7, 4.4 Hz), 4.23-4.14 (m, 1H), 4.05-4.00 (m, 1H), 3.46 (dd, 1H, J = 9.7, 8.1 Hz), 3.37 (dd, 1H, J = 9.7, 5.2 Hz), 3.30 (s, 3H), 2.22-2.11 (m, 1H), 1.38 (d, 3H, J = 6.9 Hz), 1.34 (d, 3H, J = 6.9 Hz), 0.60 (d, 3H, J = 7.3 Hz).

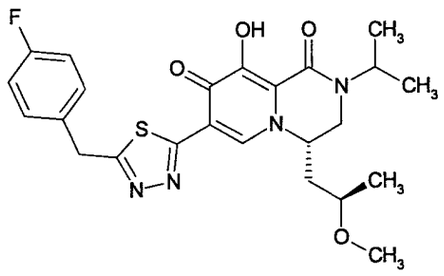
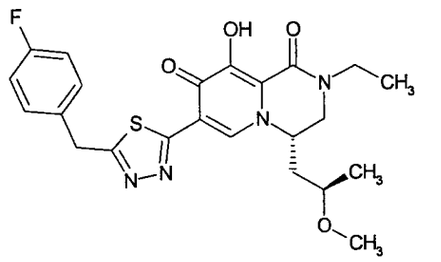
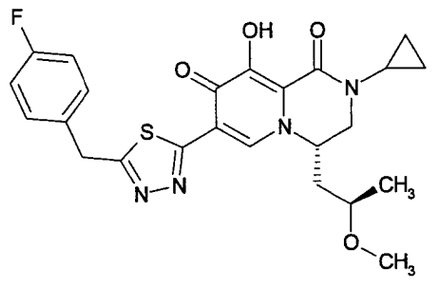
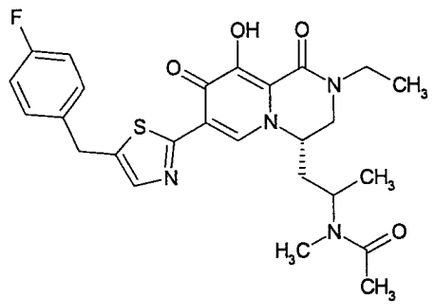
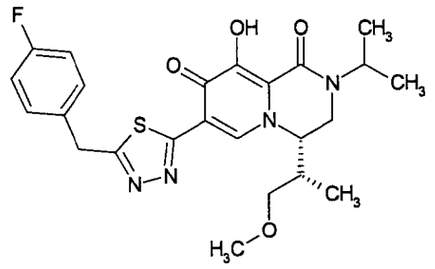
[0532]

[Table 1-116]

No.	structural formula	salt	^{1}H-NMR
448		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.42 (br s, 1H), 9.00 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.14 (m, 2H), 4.76-4.68 (m, 1H), 4.47 (s, 2H), 4.37 (dd, 1H, J = 14.1, 4.0 Hz), 4.07-3.96 (m, 1H), 3.93-3.86 (m, 1H), 3.38-3.28 (m, 2H), 3.26 (s, 3H), 3.11-2.99 (m, 1H), 2.05-1.95 (m, 1H), 1.19 (t, 3H, J = 7.1 Hz), 0.81 (d, 3H, J = 6.9 Hz).
449	 racemate, containing two kinds of diatereomers of Example No. 451	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.50 (s, 1H), 8.57 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.65-4.59 (m, 1H), 4.47 (s, 2H), 4.30-4.24 (m, 1H), 4.01-3.96 (m, 1H), 3.33-3.24 (m, 2H), 3.11 (s, 3H), 1.92-1.86 (m, 1H), 1.70 (d, 3H, J = 6.4 Hz), 1.66-1.59 (m, 1H), 1.38 (d, 3H, J = 6.9 Hz), 1.33 (d, 3H, J = 6.9 Hz).
450	 racemate, containing two kinds of diatereomers of Example No. 452	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.52 (s, 1H), 8.93 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.88-4.84 (m, 1H), 4.48 (s, 2H), 4.08-4.02 (m, 1H), 3.83 (t, 1H, J = 7.1 Hz), 3.44-3.37 (m, 2H), 3.23 (s, 3H), 3.04-2.96 (m, 1H), 1.84-1.73 (m, 2H), 1.41 (d, 3H, J = 6.9 Hz), 1.19 (t, 3H, J = 7.0 Hz).
451	 racemate, containing two kinds of diatereomers of Example No. 449	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.50 (s, 1H), 8.95 (s, 1H), 7.42-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.91 (dd, 1H, J = 12.7, 5.8 Hz), 4.61-4.54 (m, 1H), 4.48 (s, 2H), 3.88 (d, 1H, J = 8.9 Hz), 3.50-3.39 (m, 2H), 3.24 (s, 3H), 1.91-1.85 (m, 1H), 1.69-1.61 (m, 1H), 1.39 (d, 3H, J = 6.9 Hz), 1.28 (d, 3H, J = 6.4 Hz), 1.26 (d, 3H, J = 6.4 Hz).
452	 racemate, containing two kinds of diatereomers of Example No. 450	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.70 (s, 1H), 8.65 (s, 1H), 7.42-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.75-4.70 (m, 1H), 4.47 (s, 2H), 4.08-3.96 (m, 2H), 3.37-3.31 (m, 2H), 3.20 (s, 3H), 3.15-3.07 (m, 1H), 1.94-1.87 (m, 1H), 1.68-1.58 (m, 4H), 1.20 (t, 3H, J = 7.1 Hz).

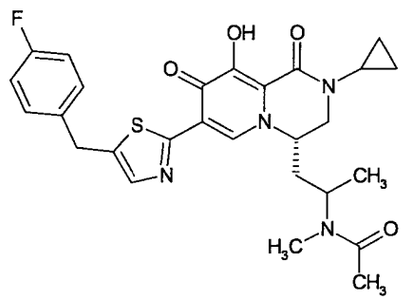
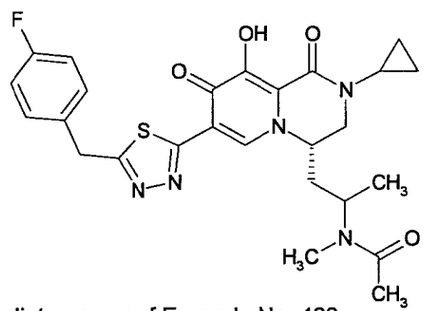
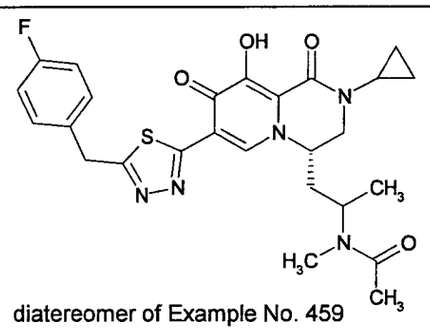
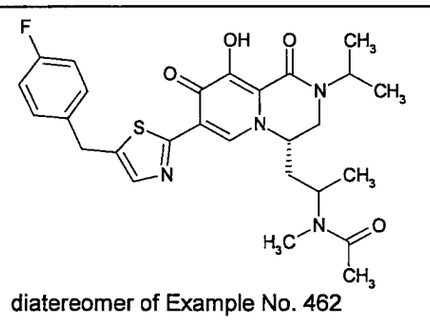
[0533]

[Table 1-117]

No.	structural formula	salt	^{1}H-NMR
453		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.72 (br s, 1H), 8.81 (s, 1H), 7.45-7.39 (m, 2H), 7.23-7.15 (m, 2H), 4.95-4.88 (m, 1H), 4.78 (sep, 1H, J = 6.9 Hz), 4.47 (s, 2H), 3.81 (dd, 1H, J = 13.5, 3.4 Hz), 3.74-3.65 (m, 1H), 3.58-3.48 (m, 1H), 3.03 (s, 3H), 1.88-1.80 (m, 1H), 1.78-1.68 (m, 1H), 1.19 (d, 3H, J = 6.9 Hz), 1.16 (d, 3H, J = 6.9 Hz), 1.07 (d, 3H, J = 6.0 Hz).
454		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.67 (br s, 1H), 8.82 (s, 1H), 7.45-7.38 (m, 2H), 7.23-7.14 (m, 2H), 4.93-4.83 (m, 1H), 4.47 (s, 2H), 4.05 (dd, 1H, J = 13.5, 3.8 Hz), 3.71-3.42 (m, 4H), 3.05 (s, 3H), 1.95-1.86 (m, 1H), 1.82-1.71 (m, 1H), 1.16 (t, 3H, J = 7.1 Hz), 1.09 (d, 3H, J = 6.0 Hz).
455		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.82 (s, 1H), 7.43-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.88-4.83 (m, 1H), 4.46 (s, 2H), 3.98 (dd, 1H, J = 13.3, 3.6 Hz), 3.53 (dd, 1H, J = 13.3, 1.8 Hz), 3.52-3.46 (m, 1H), 3.02 (s, 3H), 2.98-2.93 (m, 1H), 1.86 (ddd, 1H, J = 14.3, 6.2, 2.6 Hz), 1.71 (ddd, 1H, J = 14.3, 8.8, 7.9 Hz), 1.08 (d, 3H, J = 6.0 Hz), 0.94-0.79 (m, 3H), 0.75-0.70 (m, 1H).
456	 diatereomer of Example No. 463	HCl	^{1}H-NMR (DMSO-d_6) δ: 8.66 (s, 0.7H), 8.50 (s, 0.3H), 7.70-7.64 (m, 1.0H), 7.37-7.30 (m, 2.0H), 7.19-7.11 (m, 2.0H), 4.70-4.62 (m, 0.3H), 4.59-4.51 (m, 0.7H), 4.44-4.34 (m, 0.7H), 4.20 (s, 2.0H), 4.08-3.99 (m, 1.0H), 3.80-3.70 (m, 0.3H), 3.69-3.47 (m, 3.0H), 2.80 (s, 2.1H), 2.69 (s, 0.9H), 2.12-1.86 (m, 4.3H), 1.83-1.73 (m, 0.7H), 1.22-1.12 (m, 3.0H), 1.05 (d, 0.9H, J = 6.4 Hz), 1.00 (d, 2.1H, J = 6.4 Hz).
457		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (br s, 1H), 8.82 (s, 1H), 7.44-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.77 (sep, 1H, J = 6.9 Hz), 4.69-4.65 (m, 1H), 4.47 (s, 2H), 3.86 (d, 2H, J = 2.8 Hz), 3.37 (d, 2H, J = 5.2 Hz), 3.28 (s, 3H), 2.22-2.15 (m, 1H), 1.21 (d, 3H, J = 6.9 Hz), 1.18 (d, 3H, J = 6.9 Hz), 0.66 (d, 3H, J = 6.9 Hz).

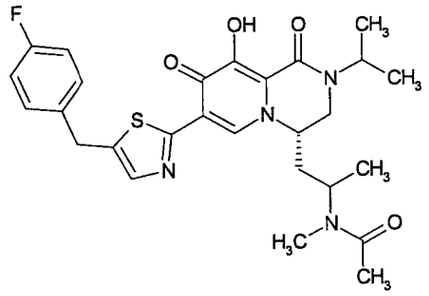
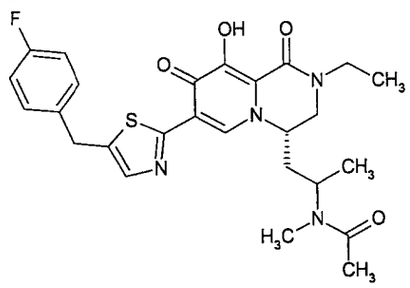
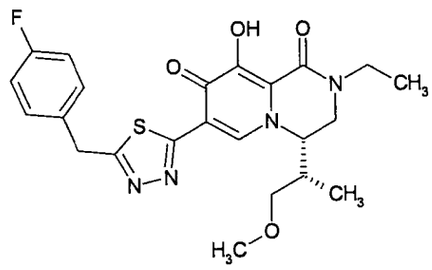
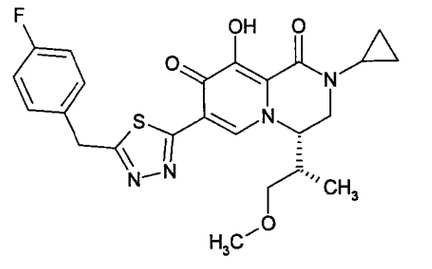
[0534]

[Table 1-118]

No.	structural formula	salt	^{1}H-NMR
458		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.63 (s, 0.67H), 8.46 (s, 0.33H), 7.71-7.61 (m, 1H), 7.39-7.28 (m, 2H), 7.21-7.10 (m, 2H), 4.67-4.31 (m, 2H), 4.26-4.16 (m, 2H), 4.07-3.42 (br m, 2H), 3.03-2.56 (br m, 4H), 2.14-1.59 (m, 5H), 1.28-0.60 (m, 7H).
459	 diatereomer of Example No. 460	HCl	^{1}H-NMR (DMSO-d_6) δ: 9.18-8.08 (m, 1H), 7.49-7.10 (m, 4H), 5.28-3.81 (m, 6H), 3.07-2.45 (m, 4H), 2.36-1.64 (m, 5H), 1.38-0.32 (m, 7H).
460	 diatereomer of Example No. 459	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.72 (br s, 1H), 8.92-8.63 (m, 1H), 7.47-7.37 (m, 2H), 7.24-7.13 (m, 2H), 4.80-4.19 (m, 4H), 4.10-3.39 (m, 2H), 3.04-2.48 (m, 4H), 2.15-1.61 (m, 5H), 1.18-0.59 (m, 7H).
461	 diatereomer of Example No. 462	HCl	^{1}H-NMR (DMSO-d_6) δ: 8.63 (s, 1H), 7.68 (s, 1H), 7.37-7.29 (m, 2H), 7.19-7.10 (m, 2H), 4.90-4.65 (m, 2H), 4.61-4.45 (m, 1H), 4.20 (s, 2H), 3.89-3.55 (m, 2H), 2.81 (s, 3H), 2.00 (s, 3H), 1.95-1.76 (m, 2H), 1.29-1.11 (br m, 6H), 1.02 (d, 3H, J = 7.1 Hz).

[0535]

[Table 1-119]

No.	structural formula	salt	^{1}H-NMR
462	 diatereomer of Example No. 461	HCl	^{1}H-NMR (DMSO-d_6) δ: 8.63 (s, 0.75H), 8.44 (s, 0.25H), 7.69-7.63 (m, 1H), 7.39-7.29 (m, 2H), 7.19-7.10 (m, 2H), 4.85-3.97 (m, 3H), 4.20 (s, 2H), 3.85-3.54 (m, 2H), 2.81 (s, 2.25H), 2.72 (s, 0.75H), 2.06-1.61 (m, 5H), 1.33-1.08 (m, 6H), 1.08-0.93 (m, 3H).
463	 diatereomer of Example No. 456	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.58 (br s, 1.0H), 8.62 (s, 0.9H), 8.58 (s, 0.1H), 7.68 (s, 0.9H), 7.67 (s, 0.1H), 7.36-7.30 (m, 2.0H), 7.18-7.11 (m, 2.0H), 4.76-4.65 (m, 1.0H), 4.57-4.49 (m, 1.0H), 4.20 (s, 2.0H), 3.99-3.93 (m, 1.0H), 3.75-3.59 (m, 1.9H), 3.59-3.38 (m, 1.1H), 2.80 (s, 2.7H), 2.58 (s, 0.3H), 1.98 (s, 2.7H), 1.92-1.83 (m, 2.3H), 1.22-1.13 (m, 3.3H), 1.03 (d, 2.7H, J = 6.9 Hz).
464		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.72 (br s, 1H), 8.81 (s, 1H), 7.44-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.65-4.62 (m, 1H), 4.47 (s, 2H), 4.09 (dd, 1H, J = 13.7, 4.0 Hz), 3.82 (dd, 1H, J = 13.7, 0.8 Hz), 3.58 (dq, 1H, J = 13.3, 7.3 Hz), 3.53 (dq, 1H, J = 13.3, 7.3 Hz), 3.37 (dd, 1H, J = 9.7, 4.8 Hz), 3.32 (dd, 1H, J = 9.7, 6.4 Hz), 3.26 (s, 3H), 2.24-2.17 (m, 1H), 1.17 (t, 3H, J = 7.3 Hz), 0.72 (d, 3H, J = 6.9 Hz).
465		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.71 (br s, 1H), 8.81 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.64-4.61 (m, 1H), 4.47 (s, 2H), 4.01 (dd, 1H, J = 13.7, 4.0 Hz), 3.72 (dd, 1H, J = 13.7, 1.2 Hz), 3.34-3.29 (m, 2H), 3.27 (s, 3H), 2.98-2.92 (m, 1H), 2.20-2.14 (m, 1H), 0.90-0.79 (m, 4H), 0.67 (d, 3H, J = 6.9 Hz).

[0536]

Experimental Example 1

The following explains evaluation methods of the HIV integrase inhibitory activity of the compound of the present invention.

[0537]

(i) Construction of recombinant integrase gene expression system

A full-length gene sequence (Accession No.: M19921) of HIV-1 pNL4-3 integrase was inserted into restriction enzyme *Nde* I and *Xho* I sites of plasmid pET21a(+) (manufactured by Novagen) to construct an integrase expression vector pET21a-IN-Wild type.

[0538]

(ii) Production and purification of integrase protein

Escherichia coli recombinant BL21(DE3) transformed with plasmid pET21a-IN-Wild type obtained in (i) was shake cultured at 30°C in a liquid medium containing ampicillin. When the culture reached the logarithmic growth phase, isopropyl-β-D-thiogalactopyranoside was added to promote expression of integrase gene. The culture was continued for 5 hr to promote accumulation of the integrase protein. The recombinant *E. coli* was collected in pellets by centrifugal separation and preserved at -80°C.

This *Escherichia coli* was suspended in Lysis buffer (50 mM Tris-HCl (pH 7.6), 10 mM $MgCl_2$, 5 mM DTT), and disrupted by repeating treatments of pressurization and depressurization, and insoluble fraction was collected by centrifugation at 4°C, 18,000 rpm for 60 min. This was suspended in Lysis buffer containing a protease inhibitor, 1.25 mM sodium chloride and 10 mM CHAPS were added, and the mixture was stirred at 4°C for 30 min. Water-soluble fraction was collected by centrifugation at 4°C, 9,000 rpm for 30 min. The obtained fraction was diluted with a column buffer (50 mM Tris-HCl (pH 7.6), 1 mM DTT, 10% Glycerol, 10 mM CHAPS) to 5-fold, and the mixture was applied to heparin column (HiPrep 16/10 Heparin FF column: manufactured by GE Healthcare Bio-Sciences). Using a column buffer containing 1M NaCl, a protein was eluted with 0-1M NaCl concentration gradient, and an eluted fraction containing an integrase protein was collected. The obtained fraction was

diluted 5-fold with a column buffer (50 mM Tris-HCl (pH 7.6), 1 mM DTT, 10% Glycerol, 10 mM CHAPS), and the mixture was applied to cation exchange column (Mono-S column: manufactured by GE Healthcare Bio-Sciences). Using a column buffer containing 1M NaCl, a protein was eluted with 0-1M NaCl concentration gradient, and an eluted fraction containing an integrase protein was collected. The obtained fractions of the integrase protein were collected, and preserved at -80°C.

[0539]

(iii) Preparation of DNA solution

The following DNA synthesized by FASMAC was dissolved in TE buffer (10 mM Tris-hydrochloric acid (pH 8.0), 1 mM EDTA) and mixed with donor DNA, target DNA, and each complementary strand (+ and - strands) to 1 μM. The mixture was heated at 95°C for 5 min, 80°C for 10 min, 70°C for 10 min, 60°C for 10 min, 50°C for 10 min and 40°C for 10 min and kept at 25°C to give a double stranded DNA, which was used for the test.

Donor DNA (+ strand having biotin attached to the 5' terminal)

Donor + strand: 5'-Biotin-ACC CTT TTA GTC AGT GTG GAA AAT CTC TAG CA-3' (SEQ ID NO:1)

Donor - strand: 5'-ACT GCT AGA GAT TTT CCA CAC TGA CTA AAA G-3' (SEQ ID NO:2)

Target DNA (+, - strands both having digoxigenin attached to the 3' terminal)

Target + strand: 5'-TGA CCA AGG GCT AAT TCA CT-Dig-3' (SEQ ID NO:3)

Target - strand: 5'-AGT GAA TTA GCC CTT GGT CA-Dig-3' (SEQ ID NO:4)

[0540]

(iv) Determination of enzyme (HIV integrase) inhibitory activity

The donor DNA was diluted with TE buffer to 20 nM, of which 50 μL was added to each well of streptavidin-coated black plate (manufactured by PIAS Corporation) and allowed to adsorb

at 37°C for 20 min. The plate was washed with phosphate buffer (Dulbecco's PBS, Sanko Junyaku Co., Ltd.) containing 0.1% Tween 20 and phosphate buffer. Then, an enzyme reaction mixture (70 μL), a test substance (10 μL) diluted with the enzyme reaction mixture and 0.75 μM integrase protein (10 μL) were added to each well and the mixture was reacted at 37°C for 60 min.

composition of enzyme reaction mixture: 30 mM MOPS (3-morpholinopropanesulfonic acid), 5 mM magnesium chloride, 3 mM DTT (dithiothreitol), 0.1 mg/mL BSA (bovine serum albumin), 5% glycerol, 10% DMSO (dimethyl sulfoxide), 0.01% Tween 20.

Then, 25 nM target DNA (10 μL) was added, and the mixture was reacted at 37°C for 20 min and washed with phosphate buffer containing 0.1% Tween 20 to stop the reaction.

Then, 100 mU/mL peroxidase labeled anti-digoxigenin antibody solution (Roche, 100 μL) was added, and the mixture was reacted at 37°C for 60 min, followed by washing with phosphate buffer containing 0.1% Tween 20.

Then, peroxidase fluorescence substrate solution (manufactured by PIAS Corporation, 100 μL) was added, and the mixture was reacted at room temperature for 20 min to 30 min. A reaction quenching liquid (manufactured by PIAS Corporation, 100 μL) was added to discontinue the reaction, and fluorescence intensity at excitation wavelength 325 nm/fluorescence wavelength 420 nm was measured.

[0541]

The HIV integrase inhibitory activity (IC_{50}) of the compound of the present invention was calculated from the inhibition rate according to the following formula:

inhibition rate (%)=[1-(Object-Blank)/(Control-Blank)]×100

Object: fluorescence intensity of well in the presence of test compound

Control: fluorescence intensity of well in the absence of test compound

Blank: fluorescence intensity of well in the absence of test compound and integrase protein

The results are shown in the following Tables.

[0542]

[Table 2-1]

Example No.	inhibitory activity IC_{50} (μM)
2	0.013
3	0.0085
4	0.01
5	0.0074
6	0.0056
7	0.013
8	0.0089
9	0.0091
10	0.0088
11	0.0064
12	0.0073
13	0.0064
14	0.01
15	0.013
16	0.02
17	0.0079
18	0.0082
19	0.0081
20	0.017

[0543]

[Table 2-2]

Example No.	inhibitory activity $IC_{50}(\mu M)$
21	0.0094
22	0.007
23	0.012
24	0.023
25	0.011
26	0.0076
27	0.01
28	0.015
29	0.01
30	0.009
31	0.0083
32	0.0077
33	0.0062
34	0.0082
35	0.0067
36	0.013
37	0.0063
38	0.012
39	0.01
40	0.013

[0544]

[Table 2-3]

Example No.	inhibitory activity IC_{50} (μM)
41	0.0072
42	0.0034
43	0.0046
44	0.0081
45	0.011
46	0.011
47	0.012
48	0.0069
49	0.0051
50	0.0064
51	0.0057
52	0.013
53	0.01
54	0.0075
55	0.021
56	0.01
57	0.011
58	0.017
59	0.012
60	0.017

[0545]

[Table 2-4]

Example No.	inhibitory activity IC_{50} (μM)
61	0.0066
62	0.0092
63	0.0083
64	0.0061
65	0.013
66	0.0064
67	0.0076
68	0.0098
69	0.013
70	0.0089
71	0.011
72	0.011
73	0.0077
74	0.0057
75	0.0091
76	0.0083
77	0.011
78	0.0089
79	0.0064
80	0.0098

[0546]

[Table 2-5]

Example No.	inhibitory activity IC_{50} (μM)
81	0.0075
82	0.0049
83	0.0071
84	0.011
85	0.0075
86	0.0095
87	0.0077
88	0.0087
89	0.008
90	0.0067
92	0.0087
93	0.0078
94	0.0088
95	0.0095
96	0.0067
97	0.0066
98	0.0075
99	0.0061
100	0.0081
101	0.0064

[0547]

[Table 2-6]

Example No.	inhibitory activity IC_{50} (μM)
102	0.0071
103	0.018
104	0.015
105	0.017
106	0.02
107	0.019
108	0.018
109	0.021
110	0.023
111	0.02
112	0.019
113	0.013
114	0.0081
115	0.012
116	0.0096
117	0.0094
118	0.013
119	0.011
120	0.015
121	0.016

[0548]

[Table 2-7]

Example No.	inhibitory activity $IC_{50}(\mu M)$
122	0.019
123	0.027
124	0.015
125	0.011
126	0.0073
127	0.014
128	0.019
129	0.012
130	0.013
131	0.013
132	0.0091
133	0.0074
134	0.016
135	0.012
136	0.011
137	0.0086
138	0.011
139	0.012
140	0.0058
141	0.008

[0549]

[Table 2-8]

Example No.	inhibitory activity IC_{50} (μM)
142	0.0064
143	0.0069
144	0.0077
145	0.0056
146	0.0059
147	0.0083
148	0.0098
149	0.0059
150	0.0061
151	0.0054
152	0.0059
153	0.0058
154	0.0073
155	0.01
156	0.0046
157	0.029
158	0.0054
159	0.0066
160	0.0061
161	0.0078

[0550]

[Table 2-9]

Example No.	inhibitory activity $IC_{50}(\mu M)$
162	0.0071
163	0.0077
164	0.0065
165	0.0074
166	0.012
167	0.01
168	0.0058
169	0.012
170	0.012
171	0.016
172	0.014
173	0.016
174	0.014
175	0.0095
176	0.0085
177	0.017
178	0.02
179	0.019
180	0.01
181	0.014

[0551]

[Table 2-10]

Example No.	inhibitory activity IC_{50} (μM)
182	0.0097
183	0.01
184	0.006
185	0.015
186	0.018
187	0.019
188	0.018
189	0.02
190	0.011
191	0.012
192	0.015
193	0.011
194	0.0082
195	0.0059
196	0.0067
197	0.014
198	0.0057
199	0.0084
200	0.0096
201	0.0095

[0552]

[Table 2-11]

Example No.	inhibitory activity $IC_{50}(\mu M)$
202	0.013
203	0.013
204	0.013
205	0.013
206	0.0059
207	0.024
208	0.012
209	0.012
210	0.023
211	0.016
212	0.014
213	0.015
214	0.016
217	0.0053
218	0.0065
219	0.015
220	0.0068
221	0.0084
222	0.0065
223	0.012

[0553]

[Table 2-12]

Example No.	inhibitory activity IC_{50} (μM)
224	0.0073
225	0.018
226	0.013
227	0.013
228	0.011
229	0.012
230	0.069
231	0.011
232	0.015
233	0.0064
234	0.018
235	0.016
236	0.013
237	0.013
238	0.018
239	0.016
240	0.052
241	0.014
242	0.013
243	0.0076

[0554]

[Table 2-13]

Example No.	inhibitory activity IC_{50} (μM)
244	0.074
245	0.0081
246	0.0084
247	0.01
248	0.014
249	0.012
250	0.017
251	0.011
252	0.0092
253	0.0077
254	0.0076
255	0.009
256	0.0082
257	0.0091
258	0.0093
259	0.009
260	0.012
261	0.011
262	0.01
263	0.009

[0555]

[Table 2-14]

Example No.	inhibitory activity IC_{50} (μM)
264	0.0085
265	0.0093
266	0.011
267	0.011
268	0.015
269	0.0094
270	0.0095
271	0.011
272	0.0089
273	0.014
274	0.012
275	0.014
276	0.016
277	0.012
278	0.0099
279	0.0063
280	0.016
281	0.016
282	0.015
283	0.018

[0556]

[Table 2-15]

Example No.	inhibitory activity IC_{50} (μM)
284	0.011
285	0.011
286	0.0078
287	0.008
288	0.0088
289	0.01
290	0.014
291	0.0087
292	0.0073
293	0.0096
294	0.011
295	0.012
296	0.019

[0557]

[Table 2-16]

Example No.	inhibitory activity IC_{50} (μM)
297	0.02
298	0.009
299	0.0098
300	0.009
301	0.008
302	0.0099
303	0.0058
304	0.0091
305	0.0095
306	0.01
307	0.011
308	0.013
309	0.0088
310	0.0099
311	0.0097
312	0.012
313	0.0097
314	0.0079
315	0.0088

[0558]

[Table 2-17]

Example No.	inhibitory activity IC_{50} (μM)
316	0.012
317	0.0098
318	0.0065
319	0.0058
320	0.0094
321	0.007
323	0.014

[0559]

[Table 2-18]

Example No.	inhibitory activity IC_{50} (μM)
327	0.0059
328	0.0071
329	0.0061
330	0.0064
331	0.0093
332	0.012
333	0.0075
334	0.0091
335	0.0098
336	0.0072
337	0.017
338	0.0071
353	0.013
354	0.0080
355	0.0066
356	0.0089
357	0.0073
358	0.012
359	0.0048
360	0.011

[0560]

[Table 2-19]

Example No.	inhibitory activity IC_{50} (μM)
361	0.015
362	0.010
363	0.0087
364	0.010
365	0.012
382	0.0087
383	0.0079
384	0.012
385	0.0082
386	0.015
387	0.011
388	0.0086
389	0.014
391	0.024
392	0.011
393	0.015
394	0.014
395	0.010
396	0.015
397	0.019

[0561]

Experimental Example 2 Evaluation of antiviral activity

The effect of combined use of the compound of the present invention and existent anti-HIV agents can be determined in the following manner.

For example, the effect of combined use of two agents from existent nucleoside reverse transcriptase inhibitors (zidovudine, lamivudine, tenofovir), non-nucleoside reverse transcriptase inhibitors (efavirenz) or protease inhibitors (indinavir, nelfinavir) and test substance A and the like are evaluated using CEM-SS cells infected with HIV-1 IIIB by XTT method.

In addition, the effect of combined use of three agents of test substance A, zidovudine and lamivudine, or test substance A, tenofovir and lamivudine, and the like is evaluated.

[0562]

Prior to the combined use test, IC_{50} and CC_{50} of each medicament alone are measured. 5 concentrates of medicament A and 9 concentrates of medicament B, determined based on these results, are combined to evaluate the effect of combined use of two agents. For combined use of three agents, a high concentrated medicament B and a medicament C are mixed and medicament A and concentration thereof are combined for evaluation.

The test results of the test substance and concomitant drug alone or in combination thereof are analyzed based on the programs of Prichard and Shipman MacSynergy II version 2.01 and Deltagraph version 1.5d. A three-dimensional plot is drawn from % inhibition at the concentrations of each combined medicament, the obtained from 3 times of tests, with 95% (or 68%, 99%) confidence limits, and the effect of the combined use is evaluated based on the numerical values of $\mu M^2\%$ calculated therefrom. The criteria of evaluation are shown in the following.

Definition of interaction	$\mu M^2\%$

Strong synergistic action	>100
Slight synergistic action	+51 - +100
Additive action	+50 - -50
Slight antagonistic action	-51 - -100
Strong antagonistic action	<-100

[0563]

Experimental Example 3 Metabolism stability test

Metabolism stability test in liver microsome

Liver microsome of human or animal species (rat or monkey) (manufactured by Xenotech LLC (Lenexa, KS, USA), 20 mg protein/mL) (2.5 μL) and NADPH-generating system coenzyme solution (β-nicotinamide adenine dinucleotide phosphate: 5.2 mM, D-glucose-6-phosphate: 13.2 mM, magnesium chloride: 13.2 mM, glucose-6-phosphate dehydrogenase: 1.8 U/mL) (50 μL) are suspended in 100 mM potassium phosphate buffer (pH 7.4, 147.5 μL), and mixed with a test substance (2 μL) dissolved in acetonitrile containing 0.5% DMSO. After incubation at 37°C for 0, 10 and 60 min, acetonitrile containing formic acid (final concentrated 0.1%) is added and the mixture is centrifuged. The test substance (unchanged form) in the supernatant is measured by high performance liquid chromatography/Mass Spectrometry (LC/MS). The residual ratio (%) is calculated from the obtained measurement values according to the following formula.

residual ratio (%) = amount of test substance after incubation (0, 10 or 60 min)/amount of test substance at incubation 0 min x 100

Preferred as the compound of the present invention is a compound with a residual ratio at 60 min later of not less than 40%, more preferably not less than 60%, further preferably not less than 80%.

[0564]

Formulation Example is given below. This example is merely for the exemplification purpose and does not limit the invention.

Formulation Example

(a)	compound of Example 1	10 g
(b)	lactose	50 g
(c)	corn starch	15 g
(d)	sodium carboxymethylcellulose	44 g
(e)	magnesium stearate	1 g

The entire amounts of (a), (b) and (c) and 30 g of (d) are kneaded with water, dried in vacuo and granulated. The obtained granules are mixed with 14 g of (d) and 1 g of (e) and processed into tablets with a tableting machine to give 1000 tablets each containing 10 mg of (a).

Industrial Applicability

[0565]

The compounds of the present invention show a high inhibitory activity against HIV integrase.

Therefore, these compounds can be medicaments effective for, for example, the prophylaxis or treatment of AIDS, as integrase inhibitors, antiviral agents, anti-HIV agents and the like, having an HIV integrase inhibitory activity. In addition, by a combined use with other anti-HIV agent(s) such as protease inhibitor, reverse transcriptase inhibitor and the like, they can be more effective anti-HIV agents. Furthermore, having high inhibitory activity specific for integrase, they can be medicaments safe for human body with a fewer side effects.

Sequence Listing Free Text

[0566]

SEQ ID NO: 1: Donor+ chain for HIV integrase activity measurement

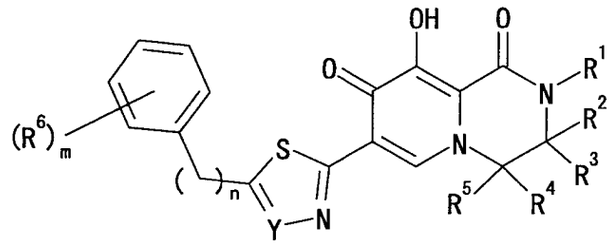
SEQ ID NO: 2: Donor- chain for HIV integrase activity measurement

SEQ ID NO: 3: Target+ chain for HIV integrase activity measurement

SEQ ID NO: 4: Target- chain for HIV integrase activity measurement

Claims

[Claim 1] A compound represented by the following formula [I] or a pharmaceutically acceptable salt thereof, or a solvate thereof:



[I]

wherein

R^1 is

(1) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from

(i) a C_{3-8} cycloalkyl group, and

(ii) a C_{1-6} alkoxy group,

(2) a C_{3-8} cycloalkyl group, or

(3) a saturated monocyclic heterocyclic group containing, besides carbon atom, 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom,

R^2, R^3, R^4 and R^5 are the same or different and each is

(1) a hydrogen atom,

(2) a carboxyl group,

(3) $-CO-NR^aR^b$ wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the following group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by

the same or different 1 to 5 substituents selected from the following group B,

(4) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the following group A, or

(5) a cyano group,

or

R^2 and R^3, or R^4 and R^5 optionally form, together with the carbon atom bonded thereto,

i) C_{3-8} cycloalkane, or

ii) a saturated monocyclic hetero ring containing, besides carbon atom, 1 to 6 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom,

wherein R^2, R^3, R^4 and R^5 are not hydrogen atoms at the same time,

R^6 is

(1) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 halogen atoms,

(2) a C_{1-6} alkoxy group,

(3) a halogen atom, or

(4) a C_{3-8} cycloalkyl group,

Y is

(1) CH, or

(2) a nitrogen atom,

m is an integer of 1 to 5, and when m is an integer of 2 to 5, then each R^6 may be the same or different, and

n is an integer of 1 to 3,

group A:

(a) $-CO-NR^{A1}R^{A2}$

wherein R^{A1} and R^{A2} are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from the following group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^{A1} and R^{A2} optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from the following group B,

(b) a hydroxyl group,

(c) a C_{1-6} alkoxy group,

(d) a C_{1-6} alkoxy-C_{1-6} alkoxy group,

(e) a cyano group,

(f) $-NR^{A3}R^{A4}$

wherein R^{A3} and R^{A4} are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group,

(iii) a C_{1-6} alkyl-carbonyl group, or

(iv) a C_{1-6} alkyl-sulfonyl group, or

R^{A3} and R^{A4} optionally form, together with the nitrogen atom bonded thereto, a hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by 1 or 2 oxo groups,

(g) a carboxyl group,

(h) a C_{1-6} alkyl-sulfonyl group, and

(i) a C_{1-6} alkyl-carbonyl group;

group B:

(a) a hydroxyl group,

(b) a C_{1-6} alkoxy group,

(c) a C_{1-6} alkoxy-C_{1-6} alkyl group

(d) a C_{3-8} cycloalkyl group, and

(e) an oxo group.

[Claim 2] The compound according to claim 1, wherein R^1 is a C_{1-6} alkyl group optionally substituted by the same or different 1

to 5 substituents selected from

(i) a C_{3-8} cycloalkyl group, and

(ii) a C_{1-6} alkoxy group,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 3] The compound according to claim 2, wherein R^1 is a C_{1-6} alkyl group, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 4] The compound according to claim 2, wherein R^1 is a C_{1-6} alkyl group substituted by a C_{3-8} cycloalkyl group, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 5] The compound according to claim 1, wherein R^1 is a C_{3-8} cycloalkyl group, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 6] The compound according to claim 1, wherein one of R^2, R^3, R^4 and R^5 is $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from group B,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 7] The compound according to claim 1, wherein one of R^2, R^3, R^4 and R^5 is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A, or a pharmaceutically acceptable salt thereof, or a solvate

thereof.

[Claim 8] The compound according to claim 1, wherein R^6 is a halogen atom, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

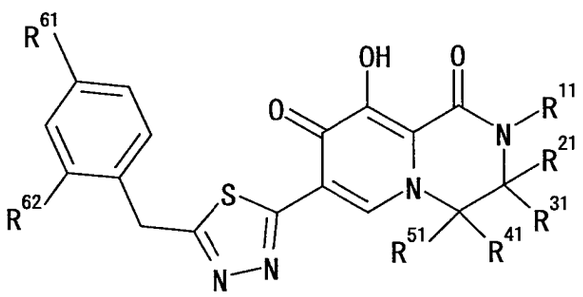
[Claim 9] The compound according to claim 1, wherein Y is CH, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 10] The compound according to claim 1, wherein Y is a nitrogen atom, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 11] The compound according to claim 1, wherein m is 1 or 2, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 12] The compound according to claim 1, wherein n is 1, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 13] The compound according to claim 1, which is represented by the following formula [I-1], or a pharmaceutically acceptable salt thereof, or a solvate thereof:



[I-1]

wherein

R^{11} is

(1) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from

(i) a C_{3-8} cycloalkyl group, and

(ii) a C_{1-6} alkoxy group, or

(2) a C_{3-8} cycloalkyl group,

R^{21}, R^{31}, R^{41} and R^{51} are the same or different and each is

(1) a hydrogen atom,

(2) $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from group B, or

(3) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A,

wherein R^{21}, R^{31}, R^{41} and R^{51} are not hydrogen atoms at the same time,

R^{61} is a halogen atom, and

R^{62} is a hydrogen atom or a halogen atom.

[Claim 14] The compound according to claim 13, wherein R^{21} is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A, and

R^{31}, R^{41} and R^{51} are each a hydrogen atom,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 15] The compound according to claim 13, wherein R^{21} is a C_{1-6} alkyl group, and

R^{31}, R^{41} and R^{51} are each a hydrogen atom,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 16] The compound according to claim 13, wherein R^{41} is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A, and

R^{21}, R^{31} and R^{51} are each a hydrogen atom,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

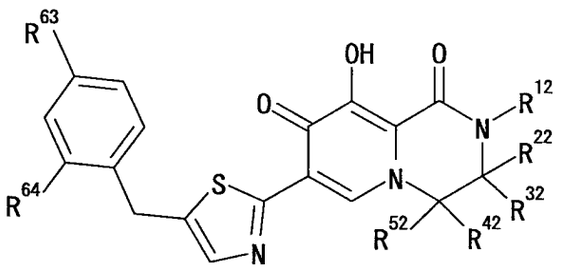
[Claim 17] The compound according to claim 13, wherein R^{21} is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A,

R^{41} is a C_{1-6} alkyl group, and

R^{31} and R^{51} are each a hydrogen atom,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 18] The compound according to claim 1, which is represented by the following formula [I-2], or a pharmaceutically acceptable salt thereof, or a solvate thereof:



[I-2]

wherein

R^{12} is a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from

(i) a C_{3-8} cycloalkyl group, and

(ii) a C_{1-6} alkoxy group,

R^{22}, R^{32}, R^{42} and R^{52} are the same or different and each is

(1) a hydrogen atom,

(2) $-CO-NR^aR^b$

wherein R^a and R^b are the same or different and each is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group B, or

(iii) a C_{3-8} cycloalkyl group, or

R^a and R^b optionally form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring

optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from group B, or

(3) a C_{1-6} alkyl group optionally substituted by the same or different 1 to 5 substituents selected from group A,

wherein R^{22}, R^{32}, R^{42} and R^{52} are not hydrogen atoms at the same time,

R^{63} is a halogen atom, and

R^{64} is a hydrogen atom or a halogen atom.

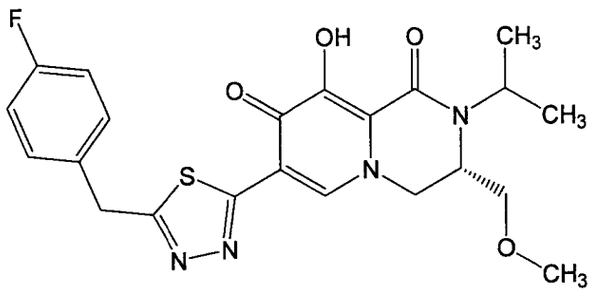
[Claim 19] The compound according to claim 18, wherein R^{42} is -CO-NR^aR^b wherein R^a and R^b form, together with the nitrogen atom bonded thereto, a saturated monocyclic hetero ring optionally containing, besides carbon atom and one nitrogen atom, 1 to 5 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally substituted by the same or different 1 to 5 substituents selected from group B,

R^{52} is a C_{1-6} alkyl group, and

R^{22} and R^{32} is a hydrogen atom,

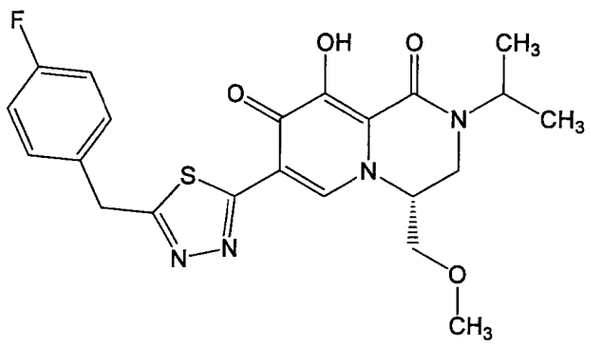
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 20] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:

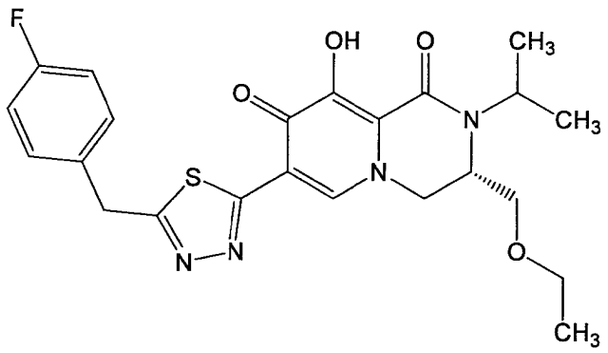


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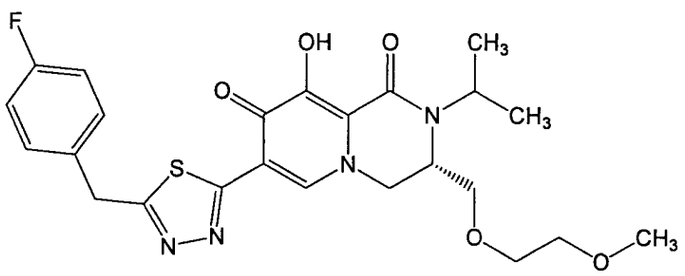
[Claim 21] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



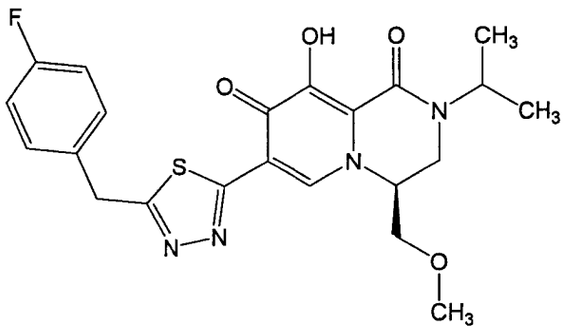
[Claim 22] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



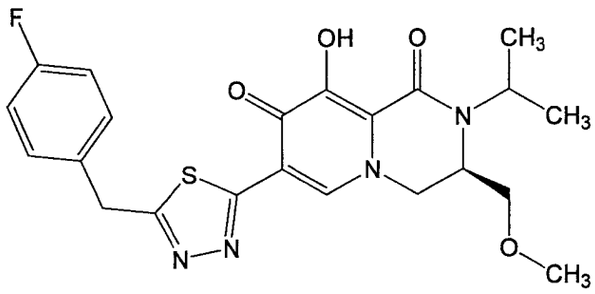
[Claim 23] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



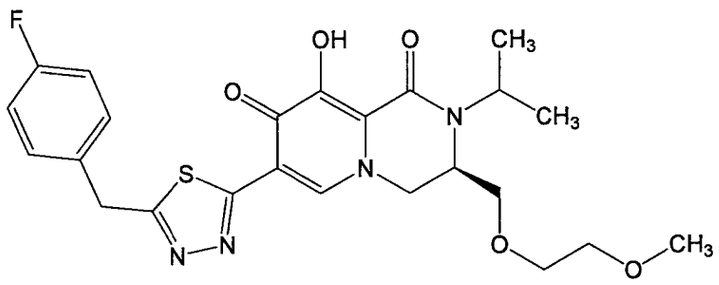
[Claim 24] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



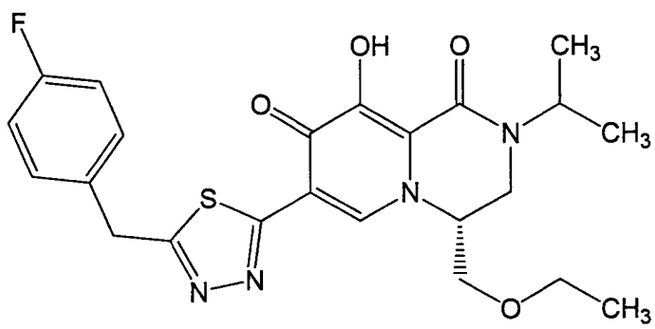
[Claim 25] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



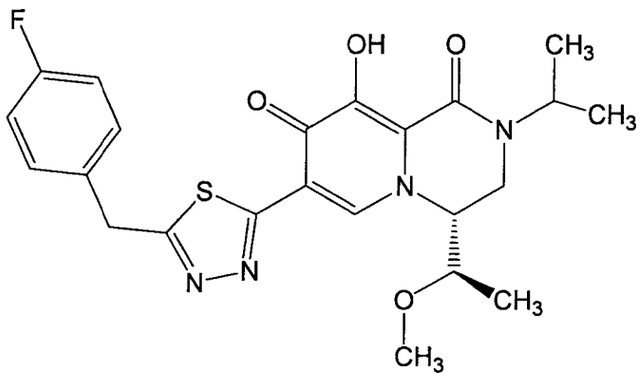
[Claim 26] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



[Claim 27] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:

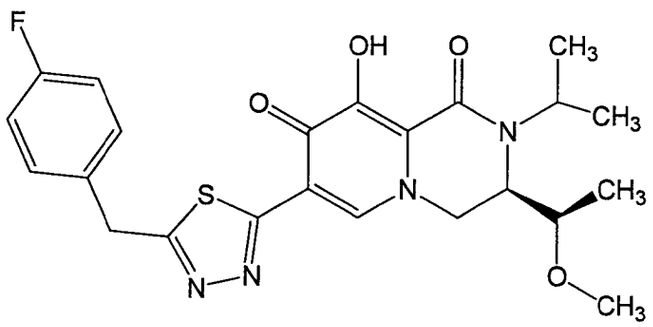


[Claim 28] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



.

[Claim 29] The compound according to claim 1, which is represented by the formula, or a pharmaceutically acceptable salt thereof, or a solvate thereof:



.

[Claim 30] A pharmaceutical composition comprising the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, and a pharmaceutically acceptable carrier.

[Claim 31] An anti-HIV agent comprising the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, as an active ingredient.

[Claim 32] An HIV integrase inhibitor comprising the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, as an active ingredient.

[Claim 33] An anti-HIV agent comprising the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, in combination with one or

more other kinds of anti-HIV active substances.

[Claim 34] Use of the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, for the production of an anti-HIV agent.

[Claim 35] Use of the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, for the production of an HIV integrase inhibitor.

[Claim 36] A method for the prophylaxis or treatment of an HIV infectious disease in a mammal, which comprises administering an effective amount of the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, to said mammal.

[Claim 37] The method according to claim 36, which further comprises administering an effective amount of one or more other kinds of anti-HIV active substances to the mammal.

[Claim 38] A method for inhibiting HIV integrase in a mammal, which comprises administering an effective amount of the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, to said mammal.

[Claim 39] An anti-HIV composition comprising the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, and a pharmaceutically acceptable carrier.

[Claim 40] A pharmaceutical composition for inhibiting HIV integrase, comprising the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof, or a solvate thereof, and a pharmaceutically acceptable carrier.

[Claim 41] A commercial package comprising the pharmaceutical composition according to claim 30 and a written matter associated therewith, which states that the pharmaceutical composition can or should be used for treating HIV.

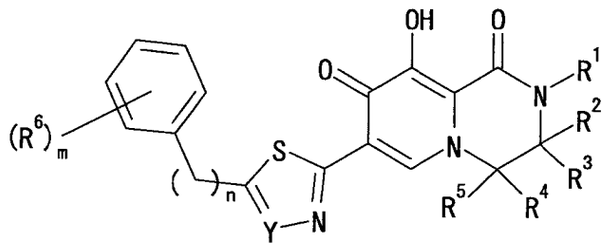
[Claim 42] A kit comprising the pharmaceutical composition

according to claim 30 and a written matter associated therewith, which states that the pharmaceutical composition can or should be used for treating HIV.

Abstract

Provided is a novel 1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrazine derivative or a pharmaceutically acceptable salt thereof, or a solvate thereof, which is useful as an anti-HIV agent.

The present invention provides a compound represented by the following formula [I]



[I]

wherein each symbol is as defined in the specification, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

SEQUENCE LISTING

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DERIVADO DE 1,3,4,8–TETRAHIDRO–2H–PIRIDO[1,2–a]PIRAZINA Y SU USO COMO INHIBIDOR DE LA INTEGRASA DEL VIH

CAMPO TÉCNICO DE LA INVENCIÓN

La presente invención se refiere a un nuevo derivado de 1,3,4,8–tetrahidro–2H–pirido[1,2–a]pirazina útil como un agente anti–VIH, una sal farmacéuticamente aceptable del mismo y un solvato del mismo. Además, la presente invención se refiere a una composición farmacéutica que comprende el derivado o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, y un portador farmacéuticamente aceptable; un agente anti–VIH, un inhibidor de la integrasa del VIH y similares, que comprende el derivado o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo como un ingrediente activo; un agente anti–VIH que comprende una combinación del derivado o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, y uno o más tipos de otras sustancias activas anti–VIH; y similares.

ANTECEDENTES DE LA INVENCIÓN

El VIH (virus de inmunodeficiencia humana (tipo 1)) que pertenece a los retrovirus es un virus causante del sida (síndrome de inmunodeficiencia adquirida).

El VIH se dirige a grupos de células CD4 positivas tales como célula T ayudante, macrófago y célula dendrítica y destruye estas células inmunocompetentes para provocar la inmunodeficiencia.

En consecuencia, un medicamento que erradica el VIH en un organismo vivo o suprime su crecimiento es efectivo para la profilaxis o el tratamiento de sida.

El VIH posee un gen de ARN bimolecular en una concha que se recubre con una proteína de envoltura. El ARN codifica varias enzimas (proteasa, transcriptasa inversa, integrasa) características del virus, y similares. La transcriptasa inversa traducida y la integrasa están presentes en la concha y la proteasa está presente dentro y fuera de la concha.

El VIH entra en contacto e invade una célula huésped, causa el descubrimiento y libera un complejo de ARN e integrasa, y similares en el citoplasma. Del ARN, el ADN se transcribe por transcriptasa inversa y se produce un ADN bicatenario de longitud completa. El ADN se mueve al núcleo de la célula huésped y es incorporado por la integrasa en el ADN de la célula huésped. El ADN incorporado es convertido en un ARNm por polimerasa de la célula huésped, de cuyo ARNm se sintetizan diversas

proteínas necesarias para formar un virus por la proteasa del VIH, y similares y finalmente se forma una partícula de virus, que luego se somete a budding y su liberación.

Se considera que estas enzimas específicas de virus son esenciales para el crecimiento del VIH. Estas enzimas requieren atención como el blanco del desarrollo de agentes antivirales y ya se han desarrollado diversos agentes anti–VIH.

Por ejemplo, ya están en el mercado zidovudina, didanosina, lamivudina, y similares como inhibidores de la transcriptasa inversa e indinavir, nelfinavir, y similares como inhibidores de la proteasa.

Además, también se emplea una terapia de combinación de múltiples fármacos usando estos medicamentos en combinación (también mencionada como HAART, por sus siglas en inglés (terapia antiretroviral muy activa)). Por ejemplo, se emplea una terapia de combinación de 3 agentes usando dos agentes de los inhibidores de la transcriptasa inversa (zidovudina y lamivudina o tenofovir y emtricitabina) y un inhibidor de la transcriptasa inversa no ácido nucleico (efavirenz) o un inhibidor de la proteasa (lopinavir, fosamprenavir o atazanavir) en combinación con ritonavir, y similares en la práctica clínica y esta terapia de combinación de múltiples fármacos se está convirtiendo en la corriente principal del tratamiento del sida.

Sin embargo, se sabe que algunos de estos medicamentos causan efectos colaterales tales como disfunción hepática, trastornos del

sistema nervioso central (por ejemplo, vértigo), y similares. Además, la adquisición de resistencia a un medicamento causa un problema. Aún peor, ya se conoce la emergencia de un VIH que muestra una resistencia a múltiples fármacos en una terapia de combinación de múltiples fármacos.

Bajo estas circunstancias, se ha deseado un desarrollo ulterior de un nuevo medicamento, en particular el desarrollo de un agente anti–VIH en base a un nuevo mecanismo, en donde se espera el desarrollo de un agente anti–VIH que tiene una actividad inhibidora de la integrasa, debido a que una característica de la integrasa de retrovirus es una enzima esencial para el crecimiento de VIH.

BREVE DESCRIPCIÓN DE LA INVENCIÓN

Problemas por resolver por la invención

De los hallazgos obtenidos a partir de estudios farmacológicos y resultados clínicos hasta la fecha, un agente anti–VIH es efectivo para la prevención o el tratamiento de sida y en particular un compuesto que tiene una actividad inhibidora de la integrasa puede ser un agente anti–VIH efectivo.

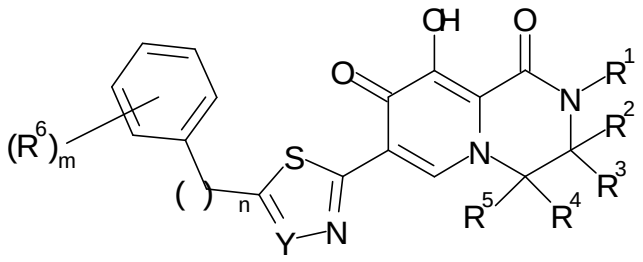
Por lo tanto, la presente invención tiene por objeto proveer un compuesto con actividad anti–VIH, en particular un compuesto con una actividad inhibidora de la integrasa.

Medios para resolver los problemas

Los presentes inventores realizaron estudios intensivos en un intento de hallar un compuesto con una acción anti–VIH, en particular un compuesto con una acción inhibidora de la integrasa y completaron la presente invención.

Más específicamente, la presente invención provee lo siguiente.

[1] Un compuesto representado por la siguiente fórmula [I] o una sal farmacéuticamente aceptable del mismo o un solvato del mismo (a veces abreviado como “el compuesto de la presente invención” en la presente memoria descriptiva):



[I]

en donde

R^1 es

(1) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de

(i) un grupo cicloalquilo de $C_{3–8}$, y

(ii) un grupo alcoxi de $C_{1–6}$,

(2) un grupo cicloalquilo de $C_{3–8}$, o

(3) un grupo heterocíclico monocíclico saturado que contiene,

además de átomos de carbono, 1 a 3 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre,

R^2, R^3, R^4 y R^5 son iguales o diferentes y cada uno es

(1) un átomo de hidrógeno,

(2) un grupo carboxilo,

(3) $–CO–NR^aR^b$, en donde R^a y R^b son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B, o

(iii) un grupo cicloalquilo de $C_{3–8}$, o

R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B,

(4) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo A, o

(5) un grupo ciano,

o

R^2 y R^3, o R^4 y R^5 forman opcionalmente, junto con el átomo de carbono al que están unidos,

i) cicloalcano de C_{3-8}, o

ii) un heteroanillo monocíclico saturado que contiene, además de átomos de carbono, 1 a 6 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre,

en donde R^2, R^3, R^4 y R^5 no son átomos de hidrógeno al mismo tiempo,

R^6 es

(1) un grupo alquilo de C_{1-6} opcionalmente sustituido con los 1 a 5 átomos de halógeno, iguales o diferentes,

(2) un grupo alcoxi de C_{1-6},

(3) un átomo de halógeno o

(4) un grupo cicloalquilo de C_{3-8},

Y es

(1) CH, o

(2) un átomo de nitrógeno,

m es un número entero de 1 a 5 y cuando m es un número entero de 2 a 5, entonces cada R^6 puede ser igual o diferente, y

n es un número entero de 1 a 3,

<u>grupo A:</u>

(a) $–CO–NR^{A1}R^{A2}$

en donde R^{A1} y R^{A2} son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B, o

(iii) un grupo cicloalquilo de $C_{3–8}$, o

R^{A1} y R^{A2} forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 3 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B,

(b) un grupo hidroxilo,

(c) un grupo alcoxi de $C_{1–6}$,

(d) un grupo alcoxi de $C_{1–6}$–alcoxi de $C_{1–6}$,

(e) un grupo ciano,

(f) $–NR^{A3}R^{A4}$

en donde R^{A3} y R^{A4} son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de $C_{1–6}$,

(iii) un grupo alquilcarbonilo de $C_{1–6}$, o

(iv) un grupo alquilsulfonilo de $C_{1–6}$, o

R^{A3} y R^{A4} forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de

oxígeno y un átomo de azufre y opcionalmente sustituido con 1 ó 2 grupos oxo,

(g) un grupo carboxilo,

(h) un grupo alquilsulfonilo de $C_{1–6}$, e

(i) un grupo alquilcarbonilo de $C_{1–6}$;

grupo B:

(a) un grupo hidroxilo,

(b) un grupo alcoxi de $C_{1–6}$,

(c) un grupo alcoxi de $C_{1–6}$–alquilo de $C_{1–6}$

(d) un grupo cicloalquilo de $C_{3–8}$ y

(e) un grupo oxo.

[2] El compuesto del punto [1] antes mencionado, en donde R^1 es un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de

(i) un grupo cicloalquilo de $C_{3–8}$ y

(ii) un grupo alcoxi de $C_{1–6}$,

o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

[3] El compuesto del punto [2] antes mencionado, en donde R^1 es un grupo alquilo de $C_{1–6}$ o una sal farmacéuticamente aceptable del mismo o un solvato del mismo.

[4] El compuesto del punto [2] antes mencionado, en donde R^1 es un grupo alquilo de $C_{1–6}$ sustituido con un grupo cicloalquilo de $C_{3–8}$ o

una sal farmacéuticamente aceptable del mismo o un solvato del mismo.

[5] El compuesto del punto [1] antes mencionado, en donde R^1 es un grupo cicloalquilo de $C_{3–8}$ o una sal farmacéuticamente aceptable del mismo o un solvato del mismo.

[6] El compuesto del punto [1] antes mencionado, en donde uno de R^2, R^3, R^4 y R^5 es $–CO–NR^aR^b$

en donde R^a y R^b son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o

(iii) un grupo cicloalquilo de $C_{3–8}$, o

R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B,

o una sal farmacéuticamente aceptable del mismo o un solvato del mismo.

[7] El compuesto del punto [1] antes mencionado, en donde uno de R^2, R^3, R^4 y R^5 es un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A,

o una sal farmacéuticamente aceptable del mismo o un solvato

del mismo.

[8] El compuesto del punto [1] antes mencionado, en donde R^6 es un átomo de halógeno o una sal farmacéuticamente aceptable del mismo o un solvato del mismo.

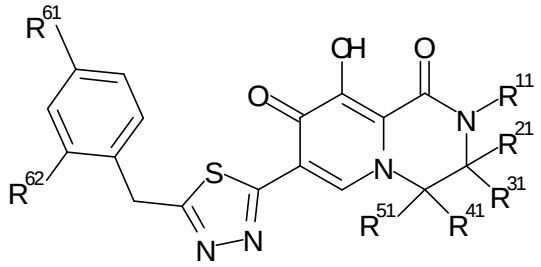
[9] El compuesto del punto [1] antes mencionado, en donde Y es CH o una sal farmacéuticamente aceptable del mismo o un solvato del mismo.

[10] El compuesto del punto [1] antes mencionado, en donde Y es un átomo de nitrógeno o una sal farmacéuticamente aceptable del mismo o un solvato del mismo.

[11] El compuesto del punto [1] antes mencionado, en donde m es 1 ó 2 o una sal farmacéuticamente aceptable del mismo o un solvato del mismo.

[12] El compuesto del punto [1] antes mencionado, en donde n es 1 o una sal farmacéuticamente aceptable del mismo o un solvato del mismo.

[13] El compuesto del punto [1] antes mencionado, que está representado por la siguiente fórmula [I–1] o una sal farmacéuticamente aceptable del mismo o un solvato del mismo:



[I-1]

en donde

R^{11} es

(1) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de

(i) un grupo cicloalquilo de $C_{3–8}$ y

(ii) un grupo alcoxi de $C_{1–6}$, o

(2) un grupo cicloalquilo de $C_{3–8}$,

R^{21}, R^{31}, R^{41} y R^{51} son iguales o diferentes y cada uno es

(1) un átomo de hidrógeno,

(2) $–CO–NR^aR^b$

en donde R^a y R^b son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o

(iii) un grupo cicloalquilo de $C_{3–8}$, o

R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o

(3) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A,

en donde R^{21}, R^{31}, R^{41} y R^{51} no son átomos de hidrógeno al mismo tiempo,

R^{61} es un átomo de halógeno y

R^{62} es un átomo de hidrógeno o un átomo de halógeno.

[14] El compuesto del punto [13] antes mencionado, en donde R^{21} es un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A y

R^{31}, R^{41} y R^{51} son cada uno un átomo de hidrógeno,

o una sal farmacéuticamente aceptable del mismo o un solvato del mismo.

[15] El compuesto del punto [13] antes mencionado, en donde

R^{21} es un grupo alquilo de C_{1-6} y

R^{31}, R^{41} y R^{51} son cada uno un átomo de hidrógeno,

o una sal farmacéuticamente aceptable del mismo o un solvato del mismo.

[16] El compuesto del punto [13] antes mencionado, en donde R^{41} es un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A, y

R^{21}, R^{31} y R^{51} son cada uno un átomo de hidrógeno,

o una sal farmacéuticamente aceptable del mismo o un solvato del mismo.

[17] El compuesto del punto [13] antes mencionado, en donde

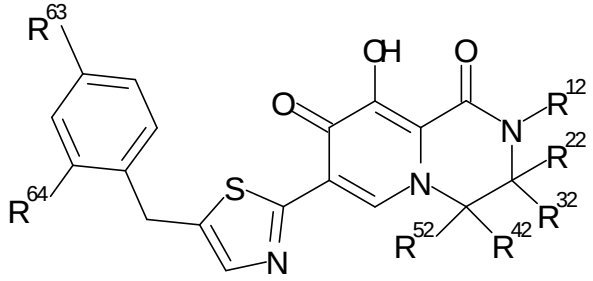
R^{21} es un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A,

R^{41} es un grupo alquilo de $C_{1–6}$ y

R^{31} y R^{51} son cada uno un átomo de hidrógeno,

o una sal farmacéuticamente aceptable del mismo o un solvato del mismo.

[18] El compuesto del punto [1] antes mencionado, que está representado por la siguiente fórmula [I–2], o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



[I-2]

en donde

R^{12} es un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de

(i) un grupo cicloalquilo de $C_{3–8}$ y

(ii) un grupo alcoxi de $C_{1–6}$,

R^{22}, R^{32}, R^{42} y R^{52} son iguales o diferentes y cada uno es

(1) un átomo de hidrógeno,

(2) $–CO–NR^aR^b$

en donde R^a y R^b son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o

(iii) un grupo cicloalquilo de $C_{3–8}$, o

R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o

(3) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A,

en donde R^{22}, R^{32}, R^{42} y R^{52} no son átomos de hidrógeno al mismo tiempo,

R^{63} es un átomo de halógeno y

R^{64} es un átomo de hidrógeno o un átomo de halógeno.

[19] El compuesto del punto [18] antes mencionado, en donde R^{42} es $–CO–NR^aR^b$

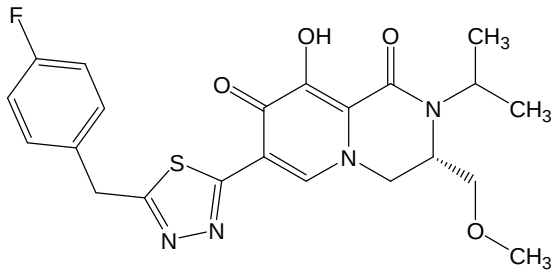
en donde R^a y R^b forman, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B,

R^{52} es un grupo alquilo de $C_{1–6}$ y

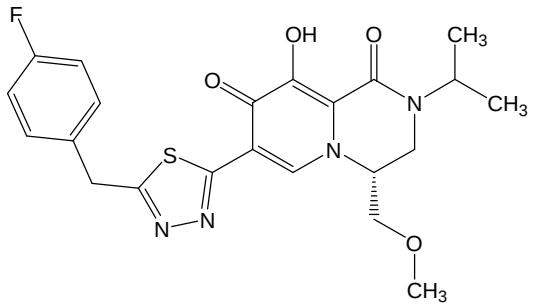
R^{22} y R^{32} es un átomo de hidrógeno,

o una sal farmacéuticamente aceptable del mismo o un solvato del mismo.

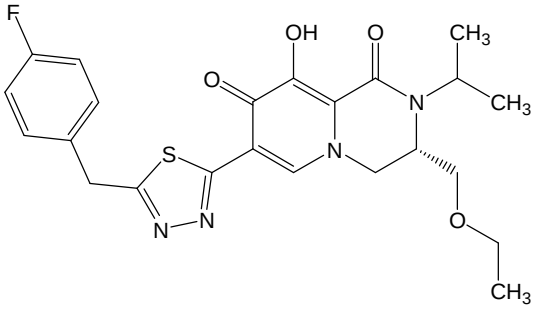
[20] El compuesto del punto [1] antes mencionado, que está representado por la fórmula o una sal farmacéuticamente aceptable del mismo o un solvato del mismo:



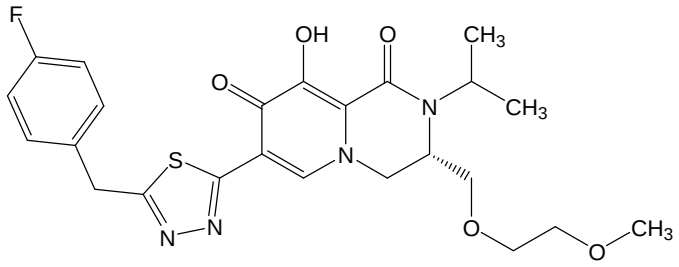
[21] El compuesto del punto [1] antes mencionado, que está representado por la fórmula o una sal farmacéuticamente aceptable del mismo o un solvato del mismo:



[22] El compuesto del punto [1] antes mencionado, que está representado por la fórmula o una sal farmacéuticamente aceptable del mismo o un solvato del mismo:

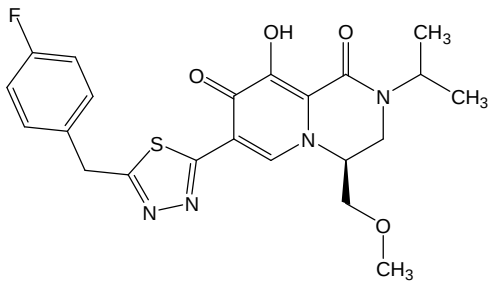


[23] El compuesto del punto [1] antes mencionado, que está representado por la fórmula o una sal farmacéuticamente aceptable del mismo o un solvato del mismo:

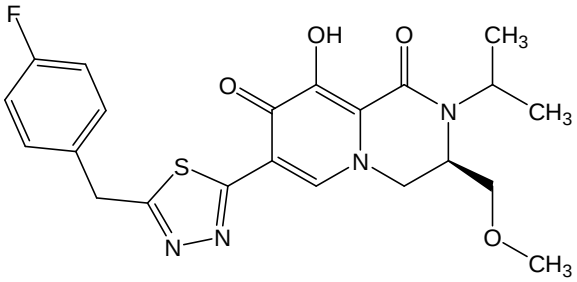


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[24] El compuesto del punto [1] antes mencionado, que está representado por la fórmula o una sal farmacéuticamente aceptable del mismo o un solvato del mismo:

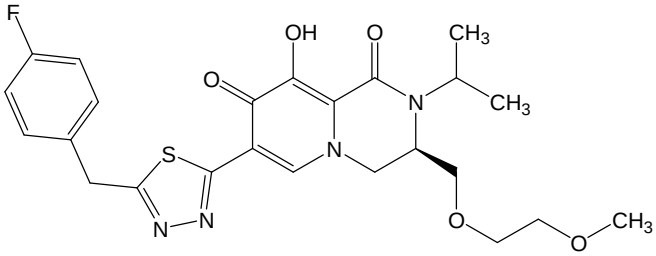


[25] El compuesto del punto [1] antes mencionado, que está representado por la fórmula o una sal farmacéuticamente aceptable del mismo o un solvato del mismo:

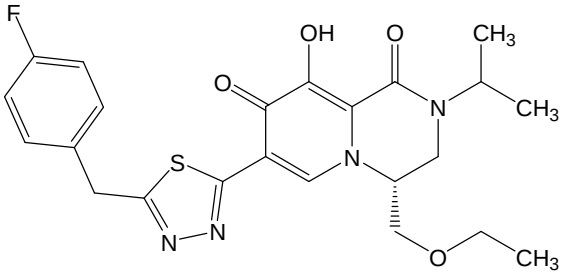


[26] El compuesto del punto [1] antes mencionado, que está representado por la fórmula o una sal farmacéuticamente aceptable del

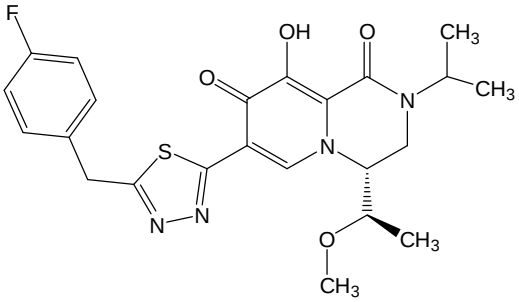
mismo o un solvato del mismo:



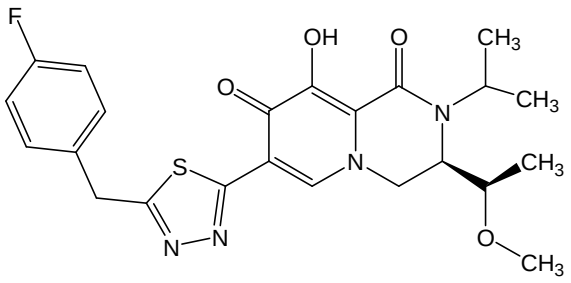
[27] El compuesto del punto [1] antes mencionado, que está representado por la fórmula o una sal farmacéuticamente aceptable del mismo o un solvato del mismo:



[28] El compuesto del punto [1] antes mencionado, que está representado por la fórmula o una sal farmacéuticamente aceptable del mismo o un solvato del mismo:



[29] El compuesto del punto [1] antes mencionado, que está representado por la fórmula o una sal farmacéuticamente aceptable del mismo o un solvato del mismo:



[30] Una composición farmacéutica que comprende el compuesto de cualquiera de los puntos [1] a [29] antes mencionados o una sal farmacéuticamente aceptable del mismo o un solvato del mismo y un portador farmacéuticamente aceptable.

[31] Un agente anti–VIH que comprende el compuesto de cualquiera de los puntos [1] a [29] antes mencionados o una sal farmacéuticamente aceptable del mismo o un solvato del mismo, como un ingrediente activo.

[32] Un inhibidor de la integrasa del VIH que comprende el compuesto de cualquiera de los puntos [1] a [29] antes mencionados o una sal farmacéuticamente aceptable del mismo o un solvato del mismo, como un ingrediente activo.

[33] Un agente anti–VIH que comprende el compuesto de cualquiera de los puntos [1] a [29] antes mencionados o una sal farmacéuticamente aceptable del mismo o un solvato del mismo, en combinación con uno o varios otros tipos de sustancias activas anti–VIH.

[34] Uso del compuesto de cualquiera de los puntos [1] a [29] antes mencionados o una sal farmacéuticamente aceptable del mismo o un

solvato del mismo, para la producción de un agente anti–VIH.

[35] Uso del compuesto de cualquiera de los puntos [1] a [29] antes mencionados o una sal farmacéuticamente aceptable del mismo o un solvato del mismo, para la producción de un inhibidor de la integrasa del VIH.

[36] Un método para la profilaxis o el tratamiento de una enfermedad infecciosa de VIH en un mamífero, que comprende la administración de una cantidad efectiva del compuesto de cualquiera de los puntos [1] a [29] antes mencionados o una sal farmacéuticamente aceptable del mismo o un solvato del mismo, a dicho mamífero.

[37] El método del punto [36] antes mencionado, que también comprende la administración de una cantidad efectiva de uno o más otros tipos de sustancias activas anti–VIH al mamífero.

[38] Un método para inhibir la integrasa del VIH en un mamífero, que comprende la administración de una cantidad efectiva del compuesto de cualquiera de los puntos [1] a [29] antes mencionados o una sal farmacéuticamente aceptable del mismo o un solvato del mismo, a dicho mamífero.

[39] Una composición anti–VIH que comprende el compuesto de cualquiera de los puntos [1] a [29] antes mencionados o una sal farmacéuticamente aceptable del mismo o un solvato del mismo y un portador farmacéuticamente aceptable.

[40] Una composición farmacéutica para inhibir la integrasa del

VIH, que comprende el compuesto de cualquiera de los puntos [1] a [29] antes mencionados o una sal farmacéuticamente aceptable del mismo o un solvato del mismo y un portador farmacéuticamente aceptable.

[41] Un envase comercial que comprende la composición farmacéutica del punto [30] antes mencionado y un material escrito asociado con la misma, que establece que la composición farmacéutica se puede o se debe usar para tratar el VIH.

[42] Un kit que comprende la composición farmacéutica del punto [30] antes mencionado y un material escrito asociado con la misma, que establece que la composición farmacéutica se puede o se debe usar para tratar el VIH.

Efecto de la invención

El compuesto de la presente invención puede ser medicamentos efectivos para la profilaxis o el tratamiento de infecciones por VIH o SIDA, como agentes anti–VIH, que tienen una actividad inhibidora de la integrasa del VIH. Además, mediante un uso combinado con otros agentes anti–VIH tales como inhibidor de la proteasa, inhibidor de la transcriptasa inversa, y similares, pueden ser agentes anti–VIH más efectivos. Adicionalmente, al tener una alta actividad inhibidora específica de la integrasa, pueden ser medicamentos seguros para el cuerpo humano con una menor cantidad de efectos colaterales.

Descripción de modalidades

Las definiciones de los respectivos sustituyentes y respectivas porciones usados en la presente especificación son las siguientes.

El “átomo de halógeno” es un átomo de flúor, un átomo de cloro, un átomo de bromo o un átomo de yodo.

El “grupo alquilo de $C_{1–6}$” es un grupo alquilo de cadena lineal o de cadena ramificada que tiene 1 a 6 átomos de carbono, con preferencia un grupo alquilo de cadena lineal o de cadena ramificada que tiene 1 a 4 átomos de carbono. Los ejemplos específicos incluyen un grupo metilo, un grupo etilo, un grupo propilo, un grupo isopropilo, un grupo butilo, un grupo isobutilo, un grupo sec–butilo, un grupo ter–butilo, un grupo pentilo, un grupo isopentilo, un grupo 1,1–dimetilpropilo, un grupo 1,2–dimetilpropilo, un grupo 2,2–dimetilpropilo, un grupo 1–etilpropilo, un grupo hexilo, y similares.

El “grupo alcoxi de $C_{1–6}$” es un grupo alcoxi de cadena lineal o de cadena ramificada que tiene 1 a 6 átomos de carbono, con preferencia un grupo alcoxi de cadena lineal o de cadena ramificada que tiene 1 a 4 átomos de carbono. Los ejemplos específicos incluyen un grupo metoxi, un grupo etoxi, un grupo propoxi, un grupo isopropiloxi, un grupo butoxi, un grupo isobutiloxi, un grupo ter–butiloxi, un grupo pentiloxi, un grupo hexiloxi, y similares.

El “grupo alcoxi de $C_{1–6}$–alquilo de $C_{1–6}$” es aquel en donde la porción alcoxi es el “grupo alcoxi de $C_{1–6}$” definido con anterioridad y la

porción de alquilo es el “grupo alquilo de $C_{1–6}$” definido con anterioridad. Se prefiere un grupo alcoxi de $C_{1–6}$–alquilo de $C_{1–6}$, en donde la porción de alcoxi es un grupo alcoxi de cadena lineal o de cadena ramificada que tiene 1 a 4 átomos de carbono y la porción de alquilo es un grupo alquilo de cadena lineal o de cadena ramificada que tiene 1 a 4 átomos de carbono. Los ejemplos del grupo alcoxi de $C_{1–6}$–alquilo de $C_{1–6}$ incluyen un grupo metoximetilo, un grupo metoxietilo, un grupo metoxipropilo, un grupo metoxibutilo, un grupo metoxipentilo, un grupo metoxihexilo, un grupo etoximetilo, un grupo etoxietilo, un grupo etoxipropilo, un grupo etoxibutilo, un grupo etoxipentilo, un grupo etoxihexilo, un grupo propoximetilo, un grupo propoxietilo, un grupo propoxipropilo, un grupo propoxibutilo, un grupo propoxipentilo, un grupo propoxihexilo, un grupo butoximetilo, un grupo butoxietilo, un grupo butoxipropilo, un grupo butoxibutilo, un grupo butoxipentilo, un grupo butoxihexilo, un grupo pentiloximetilo, un grupo pentiloxietilo, un grupo pentiloxipropilo, un grupo pentiloxibutilo, un grupo pentiloxipentilo, un grupo pentiloxihexilo, un grupo hexiloximetilo, un grupo hexiloxietilo, un grupo hexiloxipropilo, un grupo hexiloxibutilo, un grupo hexiloxipentilo, un grupo hexiloxihexilo, y similares.

El “grupo alcoxi de $C_{1–6}$–alcoxi de $C_{1–6}$” es aquel en donde la porción de alcoxi de $C_{1–6}$ es el “grupo alcoxi de $C_{1–6}$” definido con anterioridad, con preferencia un grupo alcoxi de cadena lineal o de cadena ramificada que tiene 1 a 4 átomos de carbono. Sus ejemplos incluyen un grupo metoximetoxi, un grupo metoxietoxi, un grupo metoxipropoxi, un

grupo metoxibutoxi, un grupo metoxipentiloxi, un grupo metoxihexiloxi, un grupo etoximetoxi, un grupo etoxietoxi, un grupo etoxipropoxi, un grupo etoxibutoxi, un grupo etoxipentiloxi, un grupo etoxihexiloxi, un grupo propoximetoxi, un grupo propoxietoxi, un grupo propoxipropoxi, un grupo propoxibutoxi, un grupo propoxipentiloxi, un grupo propoxihexiloxi, un grupo butoximetoxi, un grupo butoxietoxi, un grupo butoxipropoxi, un grupo butoxibutoxi, un grupo butoxipentiloxi, un grupo butoxihexiloxi, un grupo pentiloximetoxi, un grupo pentiloxietoxi, un grupo pentiloxipropoxi, un grupo pentiloxibutoxi, un grupo pentiloxipentiloxi, un grupo pentiloxihexiloxi, un grupo hexiloximetoxi, un grupo hexiloxietoxi, un grupo hexiloxipropoxi, un grupo hexiloxibutoxi, un grupo hexiloxipentiloxi, un grupo hexiloxihexiloxi, y similares.

El “grupo alquilcarbonilo de $C_{1–6}$” es un grupo alquilcarbonilo, en donde la porción de alquilo de $C_{1–6}$ es el “grupo alquilo de $C_{1–6}$” definido con anterioridad, con preferencia un grupo alquilo de cadena lineal o de cadena ramificada que tiene 1 a 4 átomos de carbono. Sus ejemplos incluyen un grupo metilcarbonilo, un grupo etilcarbonilo, un grupo propilcarbonilo, un grupo isopropilcarbonilo, un grupo butilcarbonilo, un grupo isobutilcarbonilo, un grupo sec–butilcarbonilo, un grupo ter–butilcarbonilo, un grupo pentilcarbonilo, un grupo isopentilcarbonilo, un grupo 1,1–dimetilpropilcarbonilo, un grupo hexilcarbonilo, y similares.

El “grupo alquilsulfonilo de $C_{1–6}$” es un grupo alquilsulfonilo, en donde la porción de alquilo de $C_{1–6}$ es el “grupo alquilo de $C_{1–6}$” definido

con anterioridad, con preferencia un grupo alquilo de cadena lineal o de cadena ramificada que tiene 1 a 4 átomos de carbono. Sus ejemplos incluyen un grupo metilsulfonilo, un grupo etilsulfonilo, un grupo propilsulfonilo, un grupo isopropilsulfonilo, un grupo butilsulfonilo, un grupo isobutilsulfonilo, un grupo sec–butilsulfonilo, un grupo ter–butilsulfonilo, un grupo pentilsulfonilo, un grupo isopentilsulfonilo, un grupo 1,1–dimetilpropilsulfonilo, un grupo hexilsulfonilo, y similares.

El "grupo cicloalquilo de $C_{3–8}$" es un grupo cicloalquilo saturado que tiene 3 a 8 átomos de carbono, con preferencia 3 a 5 átomos de carbono y sus ejemplos incluyen un grupo ciclopropilo, un grupo ciclobutilo, un grupo ciclopentilo, un grupo ciclohexilo, un grupo cicloheptilo, un grupo ciclooctilo, y similares.

El "cicloalcano de $C_{3–8}$" es cicloalcano saturado que tiene 3 a 8 átomos de carbono, con preferencia 3 a 5 átomos de carbono y sus ejemplos incluyen ciclopropano, ciclobutano, ciclopentano, ciclohexano, cicloheptano, ciclooctano, y similares.

El "heteroanillo" significa un heteroanillo monocíclico saturado o insaturado (incluyendo parcialmente insaturado y completamente insaturado) que contiene, además de átomos de carbono, 1 a 6 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre o un anillo fusionado de los heteroanillos, o un anillo fusionado de un anillo de carbono seleccionado de benceno, ciclopentano y ciclohexano, y el heteroanillo.

Los ejemplos del “heteroanillo monocíclico saturado que contiene, además de átomos de carbono, 1 a 6 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre” antes mencionado incluyen un heteroanillo monocíclico saturado de 4 a 7 miembros que contiene, además de átomos de carbono, 1 a 6 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y similares. Sus ejemplos específicos incluyen azetidina, pirrolidina, tetrahidrofurano, tetrahidrotiofeno, imidazolidina, pirazolidina, 1,3–dioxolano, 1,3–oxatiorano, oxazolidina, tiazolidina, piperidina, piperazina, tetrahidropirano, tetrahidrotiopirano, dioxano, morfolina, tiomorfolina, y similares.

Los ejemplos del “heteroanillo monocíclico insaturado (incluyendo parcialmente insaturado y completamente insaturado) que contiene, además de átomos de carbono, 1 a 6 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre” antes mencionado incluyen un heteroarilo monocíclico insaturado (incluyendo parcialmente insaturado y completamente insaturado) de 4 a 7 miembros que contiene, además de átomos de carbono, 1 a 6 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y similares. Sus ejemplos específicos incluyen pirrolina, furano, tiofeno, imidazol, imidazolina, pirazol, oxazol, isoxazol, tiazol, isotiazol, 1,2,4–triazol, 1,2,3–triazol, tetrazol, 1,3,4–oxadiazol, 1,2,4–oxadiazol, 1,3,4–tiadiazol, 1,2,4–tiadiazol, furazano,

piridina, pirimidina, 3,4–dihidropirimidina, piridazina, pirazina, 1,3,5–triazina, pirazolina, oxazolina, isooxazolina, tiazolina, isotiazolina, pirano, y similares.

Los ejemplos del “anillo fusionado de los heteroanillos, o anillo fusionado de un anillo de carbono seleccionados de benceno, ciclopentano y ciclohexano y el heteroanillo” antes mencionado incluyen indol, isoindol, bencimidazol, indazol, benzotiazol, benzofurano, isobenzofurano, indolizina, quinolina, isoquinolina, 1,2–dihidroquinolina, quinazolina, quinoxalina, cinolina, ftalazina, quinolizidina, purina, pteridina, indolina, isoindolina, 5,6,7,8–tetrahidroquinolina, 1,2,3,4–tetrahidroquinolina, 1,3–benzodioxolano, 3,4–metilendioxipiridina, 4,5–etilendioxipirimidina, cromeno, cromano, isocromano, 1,2,4–benzotriazina, y similares.

El “heteroanillo monocíclico saturado” formado por R^a y R^b junto con el átomo de nitrógeno al que están unidos significa un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y sus ejemplos incluyen un heteroanillo monocíclico saturado de 4 a 7 miembros (por ejemplo, de 4 a 6 miembros) que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 (por ejemplo, 1 a 3, con preferencia 1) heteroátomos seleccionados de átomo de nitrógeno, átomo de oxígeno y átomo de azufre, y similares. Los ejemplos específicos del heteroanillo monocíclico saturado incluyen

aquellos ejemplificados como el “heteroanillo monocíclico saturado que contiene, además de un átomo de carbono, 1 a 6 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre” antes mencionado, que contienen, además de un átomo de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre.

El heteroanillo monocíclico saturado está opcionalmente sustituido con 1 a 5 (por ejemplo, 1 a 3, con preferencia 1) sustituyentes iguales o diferentes seleccionados del siguiente grupo B.

El “heteroanillo monocíclico saturado” formado por R^2 y R^3 o R^4 y R^5, junto con el átomo de carbono unido a ellos significa un heteroanillo monocíclico saturado que contiene, además de átomos de carbono, 1 a 6 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y sus ejemplos incluyen un heteroanillo monocíclico saturado de 5 a 7 miembros (por ejemplo, 6 miembros) que contiene, además de átomos de carbono, 1 a 6 (por ejemplo, 1 a 3, con preferencia 1) heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y similares. Los ejemplos específicos del heteroanillo monocíclico saturado incluyen aquellos similares a los heteroanillos monocíclicos saturados ejemplificados como el “heteroanillo monocíclico saturado que contiene, además de átomos de carbono, 1 a 6 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre” antes

mencionado.

El “heteroanillo monocíclico saturado” formado por R^{A1} y R^{A2} junto con el átomo de nitrógeno al que están unidos significa un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 3 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y sus ejemplos incluyen un heteroanillo monocíclico saturado de 4 a 6 miembros que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 3 (por ejemplo, 1) heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y similares. Los ejemplos específicos del heteroanillo monocíclico saturado incluyen aquellos ejemplificados como el “heteroanillo monocíclico saturado que contiene, además de átomos de carbono, 1 a 6 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre” antes mencionado, que opcionalmente contienen, además de un átomo de carbono y un átomo de nitrógeno, 1 a 3 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre.

El heteroanillo monocíclico saturado está opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B.

El “heteroanillo” formado por R^{A3} y R^{A4} junto con el átomo de nitrógeno al que están unidos significa un heteroanillo que opcionalmente

contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y sus ejemplos incluyen un heteroanillo monocíclico de 4 a 6 miembros (por ejemplo, de 5 miembros), un heteroanillo cíclico fusionado de 8 a 10 miembros (por ejemplo, de 9 miembros), y similares, que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre. Los ejemplos específicos del heteroanillo incluyen aquellos ejemplificados como el “heteroanillo” antes mencionado, que opcionalmente contienen, además de un átomo de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre.

El heteroanillo está opcionalmente sustituido con 1 ó 2 grupos oxo.

El “grupo heterocíclico monocíclico saturado” para R^1 implica un grupo heterocíclico monocíclico saturado que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y sus ejemplos incluyen un grupo heterocíclico monocíclico saturado de 5 ó 6 miembros que contiene, además de átomos de carbono, 1 a 3 (por ejemplo, 1) heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y similares. Los ejemplos específicos del

grupo heterocíclico monocíclico saturado incluyen grupos derivados de aquellos ejemplificados como el “heteroanillo monocíclico saturado que contiene, además de átomos de carbono, 1 a 6 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre” antes mencionado, que opcionalmente contienen, además de un átomo de carbono, 1 a 3 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y similares. Sus ejemplos incluyen un grupo pirrolidinilo, un grupo tetrahidrofurilo (por ejemplo, 3–tetrahidrofurilo), un grupo tetrahidrotienilo, un grupo imidazolidinilo, un grupo pirazolidinilo, un grupo 1,3–dioxolanilo, un grupo 1,3–oxatioranilo, un grupo oxazolidinilo, un grupo tiazolidinilo, un grupo piperidinilo, un grupo piperazinilo, un grupo tetrahidropiranilo, un grupo tetrahidrotiopiranilo, un grupo dioxanilo, un grupo morfolinilo, un grupo tiomorfolinilo, y similares.

El “grupo A” incluye los siguientes sustituyentes (a) a (i).

(a) $–CO–NR^{A1}R^{A2}$

en donde R^{A1} y R^{A2} son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B, o

(iii) un grupo cicloalquilo de $C_{3–8}$, o

R^{A1} y R^{A2} forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que

opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 3 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B,

(b) un grupo hidroxilo,

(c) un grupo alcoxi de C_{1-6},

(d) un grupo alcoxi de C_{1-6}–alcoxi de C_{1-6},

(e) un grupo ciano,

(f) $-NR^{A3}R^{A4}$

en donde R^{A3} y R^{A4} son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de C_{1-6},

(iii) un grupo alquilcarbonilo de C_{1-6}, o

(iv) un grupo alquilsulfonilo de C_{1-6}, o

R^{A3} y R^{A4} forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 ó 2 grupos oxo,

(g) un grupo carboxilo,

(h) un grupo alquilsulfonilo de C_{1-6} y

(i) un grupo alquilcarbonilo de C_{1-6}.

El “grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A” es aquel en donde el “grupo alquilo de $C_{1–6}$” definido con anterioridad está opcionalmente sustituido con 1 a 5 (por ejemplo, 1 a 3, con preferencia 1) sustituyentes iguales o diferentes seleccionados de “grupo A” definido con anterioridad e incluye un grupo alquilo de $C_{1–6}$ no sustituido.

El “grupo B” incluye los siguientes sustituyentes (a) a (e).

(a) un grupo hidroxilo,

(b) un grupo alcoxi de $C_{1–6}$,

(c) un grupo alcoxi de $C_{1–6}$–alquilo de $C_{1–6}$,

(d) un grupo cicloalquilo de $C_{3–8}$ y

(e) un grupo oxo.

El “grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B” es aquel en donde el “grupo alquilo de $C_{1–6}$” definido con anterioridad está opcionalmente sustituido con 1 a 5 (por ejemplo, 1 a 3, con preferencia 1) sustituyentes iguales o diferentes seleccionados del “grupo B” definido con anterioridad e incluye un grupo alquilo de $C_{1–6}$ no sustituido.

El “heteroanillo monocíclico saturado está opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B” para R^a y R^b o R^{A1} y R^{A2} implica que el “heteroanillo monocíclico saturado” definido con anterioridad que está formado por R^a y R^b o R^{A1} y R^{A2} junto con el átomo de nitrógeno al que están unidos está

opcionalmente sustituido con 1 a 5 (por ejemplo, 1 a 3, con preferencia 1) sustituyentes iguales o diferentes seleccionados del “grupo B” definido con anterioridad e incluye un heteroanillo monocíclico saturado no sustituido.

En la fórmula [I] antes mencionada, los grupos preferidos se describen a continuación.

R^1 es

(1) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de

(i) un grupo cicloalquilo de $C_{3–8}$ y

(ii) un grupo alcoxi de $C_{1–6}$,

(2) un grupo cicloalquilo de $C_{3–8}$, o

(3) un grupo heterocíclico monocíclico saturado que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre.

La modalidad preferible de R^1 es un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de

(i) un grupo cicloalquilo de $C_{3–8}$ y

(ii) un grupo alcoxi de $C_{1–6}$.

Una modalidad de mayor preferencia de R^1 es un grupo alquilo de $C_{1–6}$.

Una modalidad diferente de mayor preferencia de R^1 es un grupo alquilo de $C_{1–6}$ sustituido con un grupo cicloalquilo de $C_{3–8}$.

Una modalidad diferente de preferencia de R^1 es un grupo cicloalquilo de $C_{3–8}$.

Otras modalidades preferibles diferentes de R^1 son

(1) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 3 grupos cicloalquilo de $C_{3–8}$ iguales o diferentes

(2) un grupo cicloalquilo de $C_{3–8}$,

(3) un grupo heterocíclico monocíclico saturado de 5 ó 6 miembros que contiene, además de átomos de carbono, 1 a 3 (por ejemplo, 1) heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y similares.

De ellos, se prefieren un grupo metilo, un grupo ciclopropilmetilo, un grupo etilo, un grupo 1–ciclopropiletilo, un grupo propilo, un grupo isopropilo, un grupo butilo, un grupo isobutilo, un grupo sec–butilo, un grupo ter–butilo, un grupo 1,2–dimetilpropilo, un grupo 2,2–dimetilpropilo, un grupo 1–etilpropilo, un grupo ciclopropilo, un grupo ciclobutilo, un grupo ciclopentilo, un grupo tetrahidrofurilo (por ejemplo, 3–tetrahidrofurilo), y similares.

R^2, R^3, R^4 y R^5 son iguales o diferentes y cada uno es

(1) un átomo de hidrógeno,

(2) un grupo carboxilo,

(3) $–CO–NR^aR^b$

en donde R^a y R^b son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo B antes mencionado o

(iii) un grupo de cicloalquilo $C_{3–8}$ o

R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo B antes mencionado,

(4) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo A antes mencionado o

(5) un grupo ciano.

En una modalidad preferida de R^2, R^3, R^4 y R^5, uno de R^2, R^3, R^4 y R^5 es $–CO–NR^aR^b$

en donde R^a y R^b son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo B antes mencionado o

(iii) un grupo cicloalquilo de $C_{3–8}$ o

R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo B antes mencionado.

En otra modalidad preferida de R^2, R^3, R^4 y R^5, uno de R^2, R^3, R^4 y R^5 es un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo A antes mencionado.

Otras modalidades preferidas de R^2, R^3, R^4 y R^5 se muestran abajo, respectivamente.

Como R^2, se prefieren

(1) un átomo de hidrógeno,

(2) un grupo carboxilo,

(3) $-CO-NR^aR^b$

en donde R^a y R^b son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno y

(ii) un grupo alquilo de C_{1-6} o

R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado de 4 a 7 miembros (por ejemplo, de 4 a 6 miembros) que opcionalmente contiene,

además de átomos de carbono y un átomo de nitrógeno, 1 a 5 (por ejemplo, 1 a 3, con preferencia 1) heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre,

(4) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 (por ejemplo, 1) sustituyentes iguales o diferentes seleccionados de

(a) $-CO-NR^{A1}R^{A2}$

en donde R^{A1} y R^{A2} son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno o

(ii) un grupo alquilo de C_{1-6},

(b) un grupo hidroxilo,

(c) un grupo alcoxi de C_{1-6},

(d) un grupo alcoxi de C_{1-6}–alcoxi de C_{1-6},

(e) un grupo ciano,

(f) $-NR^{A3}R^{A4}$

en donde R^{A3} y R^{A4} son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de C_{1-6},

(iii) un grupo alquilcarbonilo de C_{1-6} o

(iv) un grupo alquilsulfonilo de C_{1-6} y

(g) un grupo carboxilo, y

(5) un grupo ciano.

Como R^2, se prefieren más

(1) un átomo de hidrógeno,

(2) un grupo carboxilo,

(3) $–CO–NR^aR^b$

en donde R^a y R^b son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo metilo,

(ii') un grupo etilo,

(ii") un grupo isopropilo o

(ii"') un grupo ter–butilo o

R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado seleccionados de azetidina, pirrolidina y morfolina,

(4) un grupo metilo, un grupo etilo o un grupo isopropilo, que está opcionalmente sustituido con 1 a 3 (por ejemplo, 1) sustituyentes iguales o diferentes seleccionados de

(a) $–CO–NR^{A1}R^{A2}$

en donde R^{A1} y R^{A2} son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno, o

(ii) un grupo metilo,

(b) un grupo hidroxilo,

(c) un grupo metoxi,

(c') un grupo etoxi,

(c'') un grupo isopropoxi,

(d) un grupo metoxietoxi,

(e) un grupo ciano,

(f)–$NR^{A3}R^{A4}$

en donde R^{A3} y R^{A4} son iguales o diferentes y cada uno es un átomo de hidrógeno, un metilo, un grupo metilcarbonilo, un grupo isopropilcarbonilo, un grupo ter–butilcarbonilo, un grupo 1,1–dimetilpropilcarbonilo o un grupo metilsulfonilo y

(g) un grupo carboxilo, y

(5) un grupo ciano.

Como R^3, se prefieren

(1) un átomo de hidrógeno, y

(2) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con un grupo alcoxi de $C_{1–6}$.

Como R^3, se prefieren más un átomo de hidrógeno, un grupo metilo y un grupo metoximetilo.

Como R^4, se prefieren

(1) un átomo de hidrógeno,

(2) un grupo carboxilo,

(3) –CO–NR^aR^b

en donde R^a y R^b son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 (por ejemplo, 1 a 3, con preferencia 1) sustituyentes iguales o diferentes seleccionados de un grupo alcoxi de $C_{1–6}$ y un grupo cicloalquilo de $C_{3–8}$ o

(iii) un grupo cicloalquilo de $C_{3–8}$ o

R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que es un heteroanillo monocíclico saturado de 4 a 7 miembros (por ejemplo, de 4 a 6 miembros) que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 (por ejemplo, 1 a 3, con preferencia 1) heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 (por ejemplo, 1 a 3, con preferencia 1) sustituyentes iguales o diferentes seleccionados de (a) un grupo hidroxilo, (b) un grupo alcoxi de $C_{1–6}$, (c) un grupo alcoxi de $C_{1–6}$–alquilo de $C_{1–6}$ y (d) un grupo oxo,

(4) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 (por ejemplo, 1 a 3, con preferencia 1) sustituyentes iguales o diferentes

(a) $–CO–NR^{A1}R^{A2}$

en donde R^{A1} y R^{A2} son iguales o diferentes y cada uno es seleccionados de

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 (por ejemplo, 1 a 3, con preferencia 1) grupos alcoxi de $C_{1–6}$ iguales o diferentes o

(iii) un grupo cicloalquilo de $C_{3–8}$ o

R^{A1} y R^{A2} forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que es

un heteroanillo monocíclico saturado de 4 a 6 miembros que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 3 (por ejemplo, 1) heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con un grupo alcoxi de $C_{1–6}$,

(b) un grupo hidroxilo,

(c) un grupo alcoxi de $C_{1–6}$,

(d) un grupo alcoxi de $C_{1–6}$–alcoxi de $C_{1–6}$,

(e) un grupo ciano,

(f) $–NR^{A3}R^{A4}$

en donde R^{A3} y R^{A4} son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de $C_{1–6}$,

(iii) un grupo alquilcarbonilo de $C_{1–6}$, o

(iv) un grupo alquilsulfonilo de $C_{1–6}$, o

R^{A3} y R^{A4} forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo que es un heteroanillo monocíclico de 4 a 7 miembros (por ejemplo, de 6 miembros) o un heteroanillo cíclico fusionado de 8 a 10 miembros (por ejemplo, de 9 miembros) que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 ó 2 grupos oxo,

(g) un grupo carboxilo,

(h) un grupo alquilsulfonilo de $C_{1–6}$, y

(i) un grupo alquilcarbonilo de $C_{1–6}$, y

(5) un grupo ciano.

Como R^4, se prefieren más

(1) un átomo de hidrógeno,

(2) un grupo carboxilo,

(3) $–CO–NR^aR^b$

en donde R^a y R^b son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo metilo, un grupo etilo, un grupo isopropilo o un grupo isobutilo que está opcionalmente sustituido con un sustituyente igual o diferente seleccionado de un grupo metoxi y un grupo ciclopropilo o

(iii) un grupo ciclopropilo o

R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado seleccionados de azetidina, pirrolidina, piperidina y morfolina, que está opcionalmente sustituido con un sustituyente seleccionado de un grupo hidroxilo, un grupo metoxi, un grupo metoximetilo y un grupo oxo,

(4) un grupo metilo, un grupo etilo, un grupo propilo, un grupo isopropilo o un grupo ter–butilo, que está opcionalmente sustituido con un sustituyente seleccionado de

(a) $–CO–NR^{A1}R^{A2}$

en donde R^{A1} y R^{A2} son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo metilo, un grupo etilo, un grupo isopropilo o un grupo isobutilo, que está opcionalmente sustituido con un grupo metoxi o

(iii) un grupo ciclopropilo o

R^{A1} y R^{A2} forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado seleccionados de azetidina, piperidina y morfolina y opcionalmente sustituido con un grupo metoxi,

(b) un grupo hidroxilo,

(c) un grupo metoxi,

(c') un grupo etoxi,

(c") un grupo propoxi,

(c"') un grupo isopropoxi,

(c"") un grupo butoxi,

(d) un grupo metoxietoxi,

(d') un grupo etoxietoxi,

(d") un grupo metoxipropoxi,

(d"') un grupo metoxiisopropoxi,

(d"") un grupo isopropoxietoxi,

(e) un grupo ciano,

(f) $-NR^{A3}R^{A4}$

en donde R^{A3} y R^{A4} son iguales o diferentes y cada uno es un

átomo de hidrógeno, un grupo metilo, un grupo etilo, un grupo isopropilo, un grupo metilcarbonilo, un grupo etilcarbonilo, un grupo isopropilcarbonilo, un grupo metilsulfonilo o un gurpo ter–butilsulfonilo o

R^{A3} y R^{A4} forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, pirazol, triazol (por ejemplo, 1,2,4–triazol), tetrazol, oxazolidina o isoindolina, que está opcionalmente sustituido con 1 ó 2 grupos oxo,

(g) un grupo carboxilo,

(h) un grupo metilsulfonilo y

(i) un grupo metilcarbonilo y

(5) un grupo ciano.

Como R^5, se prefieren un átomo de hidrógeno y un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con un sustituyente seleccionado de un grupo alcoxi de $C_{1–6}$ y un grupo alcoxi de $C_{1–6}$–alcoxi de $C_{1–6}$.

Como R^5, se prefieren más un átomo de hidrógeno y un grupo metilo o un grupo etilo, que está opcionalmente sustituido con un sustituyente seleccionado de un grupo metoxi y un grupo metoxietoxi.

R^2 y R^3 o R^4 y R^5 forman opcionalmente, junto con el átomo de carbono al que están unidos, i) cicloalcano de $C_{3–8}$ o ii) un heteroanillo monocíclico saturado que contiene, además de átomos de carbono, 1 a 6 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre.

Como el anillo formado por R^2 y R^3 o R^4 y R^5 junto con el

átomo de carbono unido a ellos, se prefieren

i) cicloalcano de C_{3-8} y

ii) un heteroanillo monocíclico saturado de 5 a 7 miembros (por ejemplo, de 6 miembros) que contiene, además de átomos de carbono, 1 a 6 (por ejemplo, 1 a 3, con preferencia 1) heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre.

Como el anillo formado por R^2 y R^3 o R^4 y R^5 junto con el átomo de carbono unido a ellos, se prefieren más ciclopropano y tetrahidropirano.

Aquí, R^2, R^3, R^4 y R^5 no son átomos de hidrógeno al mismo tiempo.

R^6 es

(1) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 (por ejemplo, 1 a 3) átomos de halógeno iguales o diferentes,

(2) un grupo alcoxi de C_{1-6},

(3) un átomo de halógeno o

(4) un grupo cicloalquilo de C_{3-8}.

Como R^6, se prefiere un átomo de halógeno.

Otras modalidades preferidas de R^6 son un grupo metilo, un grupo trifluorometilo, un grupo metoxi, un grupo etoxi, un átomo de flúor, un átomo de cloro, un átomo de bromo y un grupo ciclopropilo.

Y es

(1) CH, o

(2) un átomo de nitrógeno.

Como Y, se prefiere CH.

Otra modalidad preferida de Y es un átomo de nitrógeno.

m es un número entero de 1 a 5 y cuando m es un número entero de 2 a 5, el R^6 antes mencionado puede ser igual o diferente.

Como m, se prefiere 1 a 3.

Como m, se prefiere más 1 ó 2.

n es un número entero de 1 a 3.

Como n, se prefiere 1.

En la fórmula antes mencionada [I–1], los grupos preferibles son como se describen a continuación.

R^{11} es

(1) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de

(i) un grupo cicloalquilo de $C_{3–8}$ y

(ii) un grupo alcoxi de $C_{1–6}$ o

(2) un grupo cicloalquilo de $C_{3–8}$.

Como R^{11}, se prefieren aquellos ejemplificados como las modalidades preferibles de R^1 en la fórmula (I) antes mencionada, que están dentro del alcance de R^{11}.

R^{21}, R^{31}, R^{41} y R^{51} son iguales o diferentes y cada uno es

(1) un átomo de hidrógeno,

(2) $–CO–NR^aR^b$

en donde R^a y R^b son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo B antes mencionado y

(iii) un grupo cicloalquilo de $C_{3–8}$ o

R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo B antes mencionado o

(3) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo A antes mencionado.

Como R^{21}, se prefiere un átomo de hidrógeno.

Otra modalidad preferida de R^{21} es un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo A antes mencionado. Se prefiere más un grupo alquilo de $C_{1–6}$.

Los ejemplos de otra modalidad preferida de R^{21} incluyen aquellos ejemplificados como las modalidades preferibles de R^2 en la

fórmula (I) antes mencionada, que están dentro del alcance de R^{21}.

Como R^{31}, se prefiere un átomo de hidrógeno.

Los ejemplos de otra modalidad preferida de R^{31} incluyen aquellos ejemplificados como las modalidades preferidas de R^3 en la fórmula (I) antes mencionada, que están dentro del alcance de R^{31}.

Como R^{41}, se prefiere un átomo de hidrógeno.

Otra modalidad preferida de R^{41} es un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo A antes mencionado. Se prefiere más un grupo alquilo de $C_{1–6}$.

Los ejemplos de otra modalidad preferida más de R^{41} incluyen aquellos ejemplificados como las modalidades preferidas de R^4 en la fórmula (I) antes mencionada, aquellos contenidos dentro del alcance de R^{41}.

Como R^{51}, se prefiere un átomo de hidrógeno.

Otras modalidades preferidas de R^{51} son aquellas ejemplificadas como las modalidades preferidas de R^5 en la fórmula (I) antes mencionada, que están dentro del alcance de R^{51}.

Aquí, R^{21}, R^{31}, R^{41} y R^{51} no son átomos de hidrógeno al mismo tiempo.

R^{61} es un átomo de halógeno.

Como R^{61}, se prefieren un átomo de flúor y un átomo de cloro.

R^{62} es un átomo de hidrógeno o un átomo de halógeno.

Como R^{62}, se prefieren un átomo de hidrógeno, un átomo de flúor y un átomo de bromo.

En la fórmula antes mencionada [I–2], los grupos preferibles son como se describen a continuación.

R^{12} es un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de

(i) un grupo cicloalquilo de $C_{3–8}$ y

(ii) un grupo alcoxi de $C_{1–6}$.

Como R^{12}, se prefieren aquellas ejemplificadas como las modalidades preferidas de R^1 en la fórmula (I) antes mencionada, que están dentro del alcance de R^{12}.

R^{22}, R^{32}, R^{42} y R^{52} son iguales o diferentes y cada uno es

(1) un átomo de hidrógeno,

(2) $–CO–NR^aR^b$

en donde R^a y R^b son iguales o diferentes y cada uno es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo B antes mencionado o

(iii) un grupo cicloalquilo de $C_{3–8}$ o

R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de

nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo B antes mencionado o

(3) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo A antes mencionado.

Como R^{22}, se prefiere un átomo de hidrógeno.

Otras modalidades preferidas de R^{22} son aquellas ejemplificadas como las modalidades preferidas de R^2 en la fórmula (I) antes mencionada, que están dentro del alcance de R^{22}.

Como R^{32}, se prefiere un átomo de hidrógeno.

Otras modalidades preferidas de R^{32} son aquellas ejemplificadas como las modalidades preferidas de R^3 en la fórmula (I) antes mencionada, que están dentro del alcance de R^{32}.

Como R^{42}, se prefiere $–CO–NR^aR^b$

en donde R^a y R^b forman, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo B antes mencionado.

Otras modalidades preferidas de R^{42} son aquellas ejemplificadas como las modalidades preferidas de R^4 en la fórmula (I) antes mencionada, que están dentro del alcance de R^{42}.

Como R^{52}, se prefiere un grupo alquilo de C_{1-6}.

Otras modalidades preferidas de R^{52} son aquellas ejemplificadas como las modalidades preferidas de R^5 en la fórmula (I) antes mencionada, que están dentro del alcance de R^{52}.

Aquí, R^{22}, R^{32}, R^{42} y R^{52} no son átomos de hidrógeno al mismo tiempo.

R^{63} es un átomo de halógeno.

Como R^{63}, se prefiere un átomo de flúor.

R^{64} es un átomo de hidrógeno o un átomo de halógeno.

Como R^{64}, se prefieren un átomo de hidrógeno y un átomo de flúor.

Como el compuesto de la presente invención, se prefieren los compuestos representados por la fórmula [I], la fórmula [I–1] y la fórmula [I–2] antes mencionadas y los compuestos descritos en los siguientes ejemplos.

Una sal farmacéuticamente aceptable de los “compuestos representados por la fórmula [I], la fórmula [I–1] y la fórmula [I–2] antes mencionadas” (de aquí en adelante también mencionado como el compuesto de la presente invención) puede ser cualquier sal mientras que forme una sal atóxica con el compuesto de la presente invención. Sus

ejemplos incluyen una sal con un ácido inorgánico, una sal con un ácido orgánico, una sal con una base inorgánica, una sal con una base orgánica, una sal con un aminoácido, y similares.

Los ejemplos del sal con un ácido inorgánico incluyen sales con ácido clorhídrico, ácido nítrico, ácido sulfúrico, ácido fosfórico, ácido bromhídrico, y similares.

Los ejemplos del sal con un ácido orgánico incluyen sales con ácido oxálico, ácido malónico, ácido maleico, ácido cítrico, ácido fumárico, ácido láctico, ácido málico, ácido succínico, ácido tartárico, ácido acético, ácido trifluoroacético, ácido glucónico, ácido ascórbico, ácido metansulfónico, ácido bencensulfónico, ácido p–toluensulfónico, y similares.

Los ejemplos de la sal con una base inorgánica incluyen sal de sodio, sal de potasio, sal de calcio, sal de magnesio, sal de amonio, y similares.

Los ejemplos del sal con una base orgánica incluyen sales con metilamina, dietilamina, trimetilamina, trietilamina, etanolamina, dietanolamina, trietanolamina, etilendiamina, tris(hidroximetil)metilamina, diciclohexilamina, N,N'–dibenciletilendiamina, guanidina, piridina, picolina, colina, cinchonina, meglumina, y similares.

Los ejemplos de la sal con un aminoácido incluyen sales con lisina, arginina, ácido aspártico, ácido glutámico, y similares.

Cada sal se puede obtener haciendo reaccionar un compuesto

representado por la fórmula [I], la fórmula [I–1] y la fórmula [I–2] con una base inorgánica, una base orgánica, un ácido inorgánico, un ácido orgánico o un aminoácido de acuerdo con un método conocido per se.

En la presente invención, como la sal farmacéuticamente aceptable de los compuestos representados por la fórmula [I], la fórmula [I–1] y la fórmula [I–2], se prefieren sales con ácido clorhídrico (por ejemplo, 1–clorhidrato, 2–clorhidrato), sales con ácido bromhídrico (por ejemplo, 1–bromhidrato, 2– bromhidrato) y sal de sodio.

El “solvato” es un compuesto representado por la fórmula [I], la fórmula [I–1] y la fórmula [I–2] o una sal farmacéuticamente aceptable del mismo, con cuya molécula de un solvente se coordina y también comprende hidratos (también mencionado como compuesto que contiene agua). El solvato es con preferencia un solvato farmacéuticamente aceptable, tales como un 1–hidrato, un 1/2–hidrato, un 2–hidrato, un 1–hidrato de sal de sodio, un 1–metanolato, un 1–etanolato, un 1–acetonitrilato, un 2/3–etanolato de 2–clorhidrato del compuesto representado por la fórmula [I], la fórmula [I–1] y la fórmula [I–2], y similares.

Un solvato de un compuesto representado por la fórmula [I], la fórmula [I–1] y la fórmula [I–2] o una sal farmacéuticamente aceptable del mismo se puede obtener de acuerdo con un método conocido per se.

Además, puede haber diversos isómeros de los compuestos representados por las fórmulas [I], [I–1] y [I–2] antes mencionadas. Por

ejemplo, cuando la forma E y la forma Z están presentes como isómeros geométricos y cuando un átomo de carbono asimétrico está presente, los enantiómeros y diastereómeros están presentes como estereoisómeros basados en ellos. Además, cuando esta presente una quiralidad, están presentes los estereoisómeros en base a ellos. De ser necesario, pueden estar presentes tautómeros. Conforme a ello, todos de tales isómeros y sus mezclas están comprendidos en el alcance de la presente invención. Como el compuesto de la presente invención, es preferible un isómero aislado y purificado de diversos isómeros, subproductos, metabolitos o profármacos y es más preferible uno que tiene una pureza no inferior al 90% y más preferible aún uno que tiene una pureza no inferior al 95%.

Además, los compuestos representados por la fórmula [I], la fórmula [I–1] y la fórmula [I–2] pueden ser cristalinos o amorfos.

Además, un compuesto representado por la fórmula [I], la fórmula [I–1] y la fórmula [I–2] puede estar rotulado con un isótopo (por ejemplo, ^{3}H, ^{14}C, ^{35}S etc.).

Como los compuestos representados por la fórmula [I], la fórmula [I–1] y la fórmula [I–2] o una sal farmacéuticamente aceptable de los mismos o un solvato de los mismos, se prefieren compuestos representados por la fórmula [I], la fórmula [I–1] y la fórmula [I–2] o una sal farmacéuticamente aceptable de los mismos o un solvato de los mismos, que están sustancialmente purificados. Se prefieren más compuestos representados por la fórmula [I], la fórmula [I–1] y la fórmula [I–2] o una sal

farmacéuticamente aceptable de los mismos o un solvato de los mismos, que se han purificado hasta una pureza no menor del 80%.

En la presente invención, un profármaco de un compuesto representado por la fórmula [I], la fórmula [I–1] y la fórmula [I–2] también puede ser un medicamento útil.

Un “profármaco” es un derivado del compuesto de la presente invención, que tiene un grupo química o metabólicamente descomponible y que se restaura en el compuesto original para mostrar su eficacia inherente después de ser administrado en el organismo, por ejemplo, por hidrólisis, solvólisis o descomposición en condiciones fisiológicas. Incluye un complejo y una sal, no incluyendo un enlace covalente.

El profármaco se utiliza, por ejemplo, para mejorar la absorción por administración oral o direccionamiento de un sitio blanco.

Los ejemplos del sitio por modificar incluyen grupos funcionales altamente reactivos en el compuesto de la presente invención, tales como grupo hidroxilo, grupo carboxilo, grupo amino, y similares.

Los ejemplos del grupo modificador del hidroxilo incluyen grupo acetilo, grupo propionilo, grupo isobutirilo, grupo pivaloílo, grupo palmitoílo, grupo benzoílo, grupo 4–metilbenzoílo, grupo dimetilcarbamoílo, grupo dimetilaminometilcarbonilo, grupo sulfo, grupo alanilo, grupo fumarilo, y similares. Además, también se puede usar una sal de sodio del grupo 3–carboxibenzoílo, grupo 2–carboxietilcarbonilo, y similares.

Los ejemplos del grupo modificador del carboxilo incluyen grupo

metilo, grupo etilo, grupo propilo, grupo isopropilo, grupo butilo, grupo isobutilo, grupo ter–butilo, grupo pivaloiloximetilo, grupo carboximetilo, grupo dimetilaminometilo, grupo 1–(acetiloxi)etilo, grupo 1–(etoxicarboniloxi)etilo, grupo 1–(isopropiloxicarboniloxi)etilo, grupo 1–(ciclohexiloxicarboniloxi)etilo, grupo (5–metil–2–oxo–1,3–dioxol–4–il)metilo, grupo bencilo, grupo fenilo, grupo o–tolilo, grupo morfolinoetilo, grupo N,N–dietilcarbamoilmetilo, grupo ftalidilo, y similares.

Los ejemplos del grupo modificador de amino incluyen grupo hexilcarbamoílo, grupo 3–metiltio–1–(acetilamino)propilcarbonilo, grupo 1–sulfo–1–(3–etoxi–4–hidroxifenil)metilo, grupo (5–metil–2–oxo–1,3–dioxol–4–il)metilo, y similares.

Los ejemplos de la “composición farmacéutica” incluyen preparaciones orales tales como comprimido, cápsula, gránulo, polvo, tableta, jarabe, emulsión, suspensión, y similares y los agentes parenterales tales como preparación externa, supositorio, inyección, gota oftálmica, agente transnasal, preparación pulmonar, y similares.

La composición farmacéutica de la presente invención (por ejemplo, una composición anti–VIH, una composición farmacéutica para la inhibición de la integrasa del VIH, etc.) se produce mezclando de manera apropiada una cantidad adecuada de un compuesto representado por la fórmula [I], la fórmula [I–1] o la fórmula [I–2] de la presente invención o una sal del mismo, o un solvato del mismo con al menos un tipo de portador farmacéuticamente aceptable de acuerdo con un método conocido per se en

el campo técnico de las preparaciones farmacéuticas. El contenido del compuesto representado por la fórmula [I], la fórmula [I–1] o la fórmula [I–2] de la presente invención o una sal del mismo, o un solvato del mismo en la composición farmacéutica varía según la forma de dosificación, la dosis, y otros, y similares. Es, por ejemplo, del 0.1 al 100% en peso de toda la composición.

Los ejemplos del “portador farmacéuticamente aceptable” incluyen diversas sustancias portadoras orgánicas o inorgánicas usadas convencionalmente como materiales de preparación tales como excipiente, disgregante, aglutinante, fluidificante, lubricante y similares para formas de dosificación sólidas, y solvente, agente de solubilización, agente de suspensión, agente de isotonicidad, agente tampón, agente suavizante, y similares para preparaciones líquidas. De ser necesario, se usan aditivos tales como conservante, antioxidante, colorante, agente endulzante, y similares.

Los ejemplos del “excipiente” incluyen lactosa, sacarosa, D–manitol, D–solbitol, almidón de maíz, dextrina, celulosa microcristalina, celulosa cristalina, carmelosa, carmelosa cálcida, carboximetilalmidón sódico, hidroxipropilcelulosa de baja sustitución, goma arábiga, y similares.

Los ejemplos del “disgregante” incluyen carmelosa, carmelosa cálcica, carmelosa sódica, carboximetilalmidón sódico, croscarmelosa sódica, crospovidona, hidroxipropilcelulosa de baja sustitución, hidroxipropilmetilcelulosa, celulosa cristalina, y similares.

Los ejemplos del “aglutinante” incluyen hidroxipropilcelulosa,

hidroxipropilmetilcelulosa, povidona, celulosa cristalina, sacarosa, dextrina, almidón, gelatina, carmelosa sódica, goma arábiga, y similares.

Los ejemplos del “fluidificante” incluyen ácido silícico anhidro liviano, estearato de magnesio, y similares.

Los ejemplos del “lubricante” incluyen estearato de magnesio, estearato de calcio, talco, y similares.

Los ejemplos del “solvente” incluyen agua purificada, etanol, propilenglicol, macrogol, aceite de sésamo, aceite de maíz, aceite de oliva, y similares.

Los ejemplos del “agente solubilizante” incluyen propilenglicol, D–manitol, benzoato de bencilo, etanol, trietanolamina, carbonato de sodio, citrato de sodio, y similares.

Los ejemplos del “agente de suspensión” incluyen cloruro de benzalconio, carmelosa, hidroxipropilcelulosa, propilenglicol, povidona, metilcelulosa, monoestearato de glicerol, y similares.

Los ejemplos del “agente isotónico” incluyen glucosa, D–sorbitol, cloruro de sodio, D–manitol, y similares.

Los ejemplos del “agente tampón” incluyen hidrógeno–fosfato de sodio, acetato de sodio, carbonato de sodio, citrato de sodio, y similares.

Los ejemplos del “agente suavizante” incluyen alcohol bencílico, y similares.

Los ejemplos del “conservante” incluyen parahidroxibenzoato de etilo, clorobutanol, alcohol bencílico, deshidroacetato de sodio, ácido

sórbico, y similares.

Los ejemplos del “antioxidante” incluyen sulfito de sodio, ácido ascórbico, y similares.

Los ejemplos del “colorante” incluyen colorantes comestibles (por ejemplo, Food Color Red No. 2 ó 3, Food Color Yellow 4 ó 5 etc.), β–caroteno, y similares.

Los ejemplos del “agente endulzante” incluyen sacarina sódica, glicirricinato dipotásico, aspartame, y similares.

La composición farmacéutica de la presente invención se puede administrar no solamente a seres humanos, sino también a mamíferos distintos de seres humanos (por ejemplo, ratón, rata, hámster, conejillo de Indias, conejo, gato, perro, cerdo, bovino, caballo, oveja, mono, etc.) por vía oral o parenteral (por ejemplo, administración tópica, rectal, intravenosa, etc.). Como la dosis varía según el sujeto de administración, la enfermedad, el síntoma, la forma de dosificación, la vía de administración, y similares, por ejemplo, la dosis para administración oral a un paciente adulto (peso corporal: aproximadamente 60 kg) está en general dentro del alcance de aproximadamente 1 mg a 1 g por día, en base al compuesto de la presente invención como un ingrediente activo. La cantidad se puede administrar en una a varias porciones.

Los compuestos representados por la fórmula [I], la fórmula [I–1] y la fórmula [I–2] antes mencionadas o una sal farmacéuticamente aceptable de los mismos o un solvato de los mismos inhiben la integrasa

del VIH y se pueden usar como un ingrediente activo de un agente terapéutico o un agente preventivo para infección por VIH.

"Inhibir la integrasa del VIH" significa inhibir específicamente la función como integrasa del VIH para eliminar o atenuar su actividad. Por ejemplo, significa inhibir específicamente la función de la integrasa del VIH en las condiciones del Ejemplo experimental 1 mencionado más abajo. Como la "inhibición de la integrasa del VIH", se prefiere la "inhibición de la integrasa del VIH humana". Como el "inhibidor de la integrasa del VIH", se prefiere un "inhibidor de la integrasa del VIH humana".

Los compuestos representados por la fórmula [I], la fórmula [I–1] y la fórmula [I–2] antes mencionados o una sal farmacéuticamente aceptable de los mismos o un solvato de los mismos se pueden usar en combinación (de aquí en adelante también mencionado como uso combinado) con otros medicamentos individuales o múltiples (de aquí en adelante también mencionado como un fármaco concomitante) por medio de un método convencional empleado generalmente en el campo de los medicamentos.

La frecuencia de administración de los compuestos representados por la fórmula [I], la fórmula [I–1] y la fórmula [I–2] antes mencionadas o una sal farmacéuticamente aceptable de los mismos o un solvato de los mismos y un fármaco concomitante no está limitada y se pueden administrar como un agente combinado a un sujeto de administración o los dos se pueden administrar simultáneamente o en

ciertos intervalos de tiempo. Además, se pueden usar como un medicamento en forma de un kit con la composición farmacéutica de la presente invención y un fármaco concomitante. La dosis del fármaco concomitante se puede determinar de acuerdo con la dosis usada clínicamente y se puede determinar apropiadamente según el sujeto de administración, la enfermedad, el síntoma, la forma de dosificación, la vía de administración, el tiempo de administración, la combinación, y similares. La forma de administración del fármaco concomitante no está limitada en particular, y el compuesto de la presente invención o una sal del mismo o un solvato del mismo y el fármaco concomitante solamente necesitan combinarse.

Un agente anti–VIH se requiere en general para sostener su efecto durante un período prolongado, de modo que pueda ser efectivo no sólo para la supresión temporal del crecimiento viral, sino también para prohibir el recrecimiento viral. Esto significa que es necesaria una administración prolongada y que una dosis única alta puede ser con frecuencia inevitable para mantener el efecto durante un período prolongado en la noche. Esta administración de dosis prolongada y elevada aumenta el riesgo de efectos colaterales.

En vista de ello, una de las modalidades preferidas del compuesto de la presente invención es aquel compuesto que permite una alta absorción por administración oral y aquel compuesto que es capaz de mantener una concentración en sangre del compuesto administrado

durante un largo período.

Además de lo mencionado anteriormente, las modalidades preferidas del compuesto de la presente invención son un compuesto que tiene una actividad farmacológica fina (por ejemplo, un compuesto que tiene una fuerte actividad inhibidora de la integrasa del VIH, un compuesto que tiene alta actividad anti–VIH), un compuesto que tiene una biodisponibilidad fina (por ejemplo, un compuesto que tiene alta permeabilidad de membrana celular, un compuesto estable a la enzima metabólica, un compuesto con baja capacidad de unión con la proteína, y similares), un compuesto con actividad anti–VIH contra VIH que tiene mutación G140S/Q148H, y similares.

De los compuestos de la presente invención, se prefiere un compuesto que tiene alta actividad farmacológica (en concreto, la IC_{50} de actividad inhibidora de la integrasa del VIH es inferior a 0.1 μM, con preferencia inferior a 0.01 μM) y se prefiere más una alta absorción oral, cuya concentración en sangre se mantiene durante un tiempo prolongado después de la administración.

Usando el compuesto antes mencionado, se espera que la dosis y/o la frecuencia de administración del compuesto de la presente invención a seres humanos se reduzcan. La frecuencia de administración preferida no es mayor a dos veces por día, con mayor preferencia, no más de una vez por día (por ejemplo, una vez por día, una vez cada dos días, etc.).

El compuesto de la presente invención se puede usar para mejorar la viremia debida a VIH y/o mantener su condición mejorada, profilaxis y tratamiento de infecciones virales, en particular, una infección por VIH y/o mantener su condición mejorada.

Como un índice de “tratamiento”, “mejora” o “efecto”, se puede usar una reducción del nivel viral o del nivel de ARN de VIH en el organismo, en particular en sangre.

La “profilaxis de la infección por VIH” incluye la administración de un medicamento a una persona con sospecha o posibilidad de una infección por VIH (infección debida a transfusión, infección de madre a hijo), y similares.

Por “profilaxis del SIDA” se entiende, por ejemplo, la administración de un medicamento a un individuo cuya prueba dio VIH positivo pero que aún no ha desarrollado el estado patológico del SIDA; la administración de un medicamento a un individuo que muestra un estado patológico mejorado del SIDA después del tratamiento pero que porta VIH aún por erradicar y del que se teme una recaída por SIDA; la administración de un medicamento antes de la infección con VIH sin temor de posible infección; y similares.

Los ejemplos de “otros agentes anti–VIH” y “otras sustancias activas anti–VIH” para usar para una terapia de combinación de múltiples fármacos incluyen un anticuerpo anti–VIH u otro anticuerpo, una vacuna VIH u otra vacuna, inmunoestimulantes tales como interferón, agonista de

interferón, y similares, una ribozima contra VIH, un fármaco antisentido del VIH, un inhibidor de la transcriptasa inversa del VIH, un inhibidor de la proteasa del VIH, un inhibidor de la integrasa del VIH, un inhibidor de unión entre un receptor (CD4, CXCR4, CCR5, y similares) de una célula huésped reconocida por virus y el virus (antagonista de CCR5, y similares), un inhibidor de ADN polimerasa o un inhibidor de la síntesis de ADN, un medicamento que actúa sobre VIHp24, un inhibidor de la fusión de VIH, un agonista o antagonista de IL–2, un antagonista de TNF–α, un inhibidor de α–glucosidasa, un inhibidor de la purina nucleósido fosforilasa, un agonista o inhibidor de la apoptosis, un inhibidor de la colinesterasa, un inmunomodulador, y similares.

Los ejemplos específicos del inhibidor de la transcriptasa inversa del VIH incluyen Retrovir(R) (zidovudina), Epivir(R) (lamivudina), Zerit(R) (sanilvudina), Videx(R) (didanosina), Hivid(R) (zalcitabine), Ziagen(R) (sulfato de abacavir), Viramune(R) (nevirapina), Stocrin(R) (efavirenz), Rescriptor(R) (mesilato de delavirdina), Combivir(R) (zidovudina + lamivudina), Trizivir(R) (sulfato de abacavir + lamivudina + zidovudina), Coactinon(R) (emivirina), Phosfonovir(R), Coviracil(R), alovudina (3'–fluoro–3'–desoxitimidina), Thiovir (ácido tiofosfonofórmico), Capravirin (ácido 5–[(3,5–diclorofenil)tio]–4–isopropil–1–(4–piridilmetil)imidazol–2–metanolcarbámico), disoproxilfumarato de Tenofovir (bis(isopropoxicarboniloximetil)éster fumarato de ácido (R)–[[2–(6–amino–9H–purin–9–il)–1–metiletoxi]metil]fosfónico), DPC–083 ((4S)–6–cloro–4–

[(1E)–ciclopropiletenil]–3,4–dihidro–4–trifluorometil–2(1H)–quinazolinona), DPC–961 ((4S)–6–cloro–4–(ciclopropiletinil)–3,4–dihidro–4–(trifluorometil)–2(1H)–quinazolinona), DAPD ((–)–β–D–2,6–diaminopurina dioxolano), Immunocal, MSK–055, MSA–254, MSH–143, NV–01, TMC–120, DPC–817, GS–7340, TMC–125, SPD–754, D–A4FC, capravirina, UC–781, emtricitabina, alovudina, fosfazida, BCH–10618, DPC–083, Etravirina, BCH–13520, MIV–210, sulfato de abacavir/lamivudina, GS–7340, GW–5634, GW–695634, TMC-278 y similares, en donde (R) significa marca registrada (de aquí en adelante, las mismas) y los nombres de otros medicamentos son nombres generales.

Los ejemplos específicos del inhibidor de la proteasa del VIH incluyen Crixivan(R) (sulfato etanolato de indinavir), saquinavir, Invirase(R) (mesilato de saquinavir), Norvir(R) (ritonavir), Viracept(R) (mesilato de nelfinavir), lopinavir, Prozei(R) (amprenavir), Kaletra(R) (ritonavir + lopinavir), dimesilato de mozenavir (dimetansulfonato de [4R–(4α,5α,6β)]–1,3–bis[(3–aminofenil)metil]hexahidro–5,6–dihidroxi–4,7–bis(fenilmetil)–2H–1,3–diazepin–2–ona), tipranavir (3'–[(1R)–1–[(6R)–5,6–dihidro–4–hidroxi–2–oxo–6–feniletil–6–propil–2H–piran–3–il]propil]–5–(trifluorometil)–2–piridinsulfonamida), lasinavir (2–metoxietilenamida de N–[5(S)–(ter–butoxicarbonilamino)–4(S)–hidroxi–6–fenil–2(R)–(2,3,4–trimetoxibencil)hexanoil]–L–valina), KNI–272 ((R)–N–ter–butil–3–[(2S,3S)–2–hidroxi–3–N–[(R)–2–N–(isoquinolin–5–iloxiacetil)amino–3–metiltiopropanoil]amino–4–fenilbutanoil]–5,5–dimetil–1,3–tiazolidin–4–

carboxamida), GW–433908, TMC–126, DPC–681, buckminsterfulereno, MK–944A (MK944 (N–(2(R)–hidroxi–1(S)–indanil)–2(R)–fenilmetil–4(S)–hidroxi–5–[4–(2–benzo[b]furanilmetil)–2(S)–(ter–butilcarbamoil)piperazin–1–il]pentanamida) + sulfato de indinavir), JE–2147 ([2(S)–oxo–4–fenilmetil–3(S)–[(2–metil–3–oxi)fenilcarbonilamino]–1–oxabutil]–4–[(2–metilfenil)metilamino]carbonil–4(R)–5,5–dimetil–1,3–tiazol), BMS–232632 ((3S,8S,9S,12S)–3,12–bis(1,1–dimetiletil)–8–hidroxi–4,11–dioxo–9–(fenilmetil)–6–[[4–(2–piridinil)fenil]metil]–2,5,6,10,13–pentaazatetradecandicarboxilato de dimetilo), DMP–850 ((4R,5S,6S,7R)–1–(3–amino–1H–indazol–5–ilmetil)–4,7–dibencil–3–butil–5,6–dihidroxiperhidro–1,3–diazepin–2–ona), DMP–851, RO–0334649, Nar–DG–35, R–944, VX–385, TMC–114, Tipranavir, Fosamprenavir sodio, Fosamprenavir calcio, Darunavir, GW–0385, R–944, RO–033–4649, AG–1859, y similares.

El inhibidor de la integrasa del VIH está ejemplificado por S–1360, L–870810, y similares, el inhibidor de la ADN polimerasa o inhibidor de la síntesis de ADN está ejemplificado por Foscavir(R), ACH–126443 (L–2',3'–didehidro–didesoxi–5–fluorocitidina), entecavir ((1S,3S,4S)–9–[4–hidroxi–3–(hidroximetil)–2–metileneciclopentil]guanina), calanolide A ([10R–(10α,11β,12α)]–11,12–dihidro–12–hidroxi–6,6,10,11–tetrametil–4–propil–2H,6H,10H–benzo[1,2–b:3,4–b':5,6–b"]tripiran–2–ona), calanolide B, NSC–674447 (1,1'–azobisformamida), Iscador (extracto de viscum album), Rubitecan, y similares, el fármaco antisentido de VIH está ejemplificado por

HGTV–43, GEM–92, y similares, el anticuerpo anti–VIH u otro anticuerpo está ejemplificado por NM–01, PRO–367, KD–247, Cytolin(R), TNX–355 (anticuerpo CD4), AGT–1, PRO–140 (anticuerpo CCR5), Anti–CTLA–4MAb, y similares, la vacuna del VIH u otra vacuna está ejemplificada por ALVAC(R), AIDSVAX(R), Remune(R), vacuna VIH gp41, vacuna VIH gp120, vacuna VIH gp140, vacuna VIH gp160, vacuna VIH p17, vacuna VIH p24, vacuna VIH p55, AlphaVax Vector System, vacuna canaripox gp160, AntiTat, vacuna MVA–F6 Nef, vacuna VIH rev, péptido C4–V3, p2249f, VIR–201, HGP–30W, TBC–3B, PARTICLE–3B, Antiferon (vacuna de interferón–α), y similares, el interferón o agonista de interferón está ejemplificado por Sumiferon(R), MultiFeron(R), interferón–τ, Reticulose, interferón α de leucocito humano, y similares, el antagonista de CCR5 está ejemplificado por SCH–351125, y similares, el medicamento que actúa sobre VIH p24 está ejemplificado por GPG–NH2 (glicil–prolil–glicinamida), y similares, el inhibidor de fusión de VIH está ejemplificado por FP–21399 (1,4–bis[3–[(2,4–diclorofenil)carbonilamino]–2–oxo–5,8–disodio sulfonil]naftil–2,5–dimetoxifenil–1,4–dihidrazona), T–1249, construcción polimérica sintética No. 3, pentafusida, FP–21399, PRO–542, Enfuvirtide, y similares, el agonista o antagonista de IL–2 está ejemplificado por interleuquina–2, Imunace(R), Proleukin(R), Multikine(R), Ontak(R), y similares, el antagonista de TNF–α está ejemplificado por Thalomid(R) (talidomida), Remicade(R) (infliximab), sulfato de curdlan, y similares, el

inhibidor de α–glucosidasa está ejemplificado por Bucast(R), y similares, el inhibidor de purina nucleósido fosforilasa está ejemplificado por peldesina (2–amino–4–oxo–3H,5H–7–[(3–piridil)metil]pirrolo[3,2–d]pirimidina), y similares, el agonista o inhibidor de la apoptosis está ejemplificado por Arkin Z(R), Panavir(R), Coenzima Q10 (2–deca(3–metil–2–butenilen)–5,6–dimetoxi–3–metil–p–benzoquinona) y similares, el inhibidor de colinesterasa está ejemplificado por Cognex(R), y similares y el inmunomodulador está ejemplificado por Imunox(R), Prokine(R), Met–encefalina (6–de–L–arginina–7–de–L–arginina–8–de–L–valinamida–adrenorfina), WF–10 (solución decadiluida de tetraclorodecaóxido), Perton, PRO–542, SCH–D, UK–427857, AMD–070, AK–602, TK-303 (Elvitegravir) y similares.

Además, se ejemplifican Neurotropin(R), Lidakol(R), Ancer 20(R), Ampligen(R), Anticort(R), Inactivin(R), PRO–2000, gen Rev M10, célula T citotóxica específica de VIH (CTL immunotherapy, ACTG protocol 080 therapy, CD4–ζ gene therapy), proteína de unión a SCA, complejo RBC–CD4, Motexafin gadolinio, GEM–92, CNI–1493, (±)–FTC, Ushercell, D2S, BufferGel(R), VivaGel(R), gel vaginal Glyminox, laurilsulfato sódico, 2F5, 2F5/2G12, VRX–496, Ad5gag2, BG–777, IGIV–C, BILR–255, y similares.

El compuesto de la presente invención se puede combinar con uno o más (por ejemplo, 1 ó 2) tipos de otras sustancias activas anti–VIH (también mencionadas como otros agentes anti–VIH) y se pueden usar

como un agente anti–VIH, y similares para la profilaxis o el tratamiento de infección por VIH. Como los “otros agentes anti–VIH” y “otras sustancias activas anti–VIH” para usar para una terapia de combinación de múltiples fármacos con el compuesto de la presente invención, se prefieren un inhibidor de la transcriptasa inversa del VIH y un inhibidor de la proteasa del VIH. Dos o tres o incluso un número mayor de medicamentos se puede usar en combinación, en donde una combinación de medicamentos con diferentes mecanismos de acción es una de las modalidades preferidas. Además, es preferible una selección de medicamentos libres de duplicación de efectos colaterales.

Los ejemplos específicos de la combinación de medicamentos incluyen una combinación de un grupo que consiste en efavirenz, tenofovir, emtricitabina, indinavir, nelfinavir, atazanavir, ritonavir + indinavir, ritonavir + lopinavir, ritonavir + saquinavir, didanosina + lamivudina, zidovudina + didanosina, estavudina + didanosina, zidovudina + lamivudina, estavudina + lamivudina y tenofovir + emtricitabina, y el compuesto de la presente invención (Guidelines for The Use of Antiretroviral Agents in VIH–Infected Adults and Adolescents. August 13, 2001). Se prefiere en particular un uso combinado de dos agentes con efavirenz, indinavir, nelfinavir, tenofovir, emtricitabina, zidovudina o lamivudina, y un uso combinado de tres agentes con zidovudina + lamivudina, tenofovir + lamivudina, tenofovir + zidovudina, tenofovir + efavirenz, tenofovir + nelfinavir, tenofovir + indinavir, tenofovir + emtricitabina, emtricitabina + lamivudina, emtricitabina + zidovudina,

emtricitabina + efavirenz, emtricitabina + nelfinavir, emtricitabina + indinavir, nelfinavir + lamivudina, nelfinavir + zidovudina, nelfinavir + efavirenz, nelfinavir + indinavir, efavirenz + lamivudina, efavirenz + zidovudina o efavirenz + indinavir.

En el caso de una administración combinada, el compuesto de la presente invención se puede administrar simultáneamente con un medicamento para usarse en combinación (de aquí en adelante, fármaco concomitante) o se puede administrar a intervalos de tiempo determinados. En el caso de una administración combinada, se puede administrar una composición farmacéutica que comprende el compuesto de la presente invención y un fármaco concomitante. De modo alternativo, se pueden administrar una composición farmacéutica que comprende el compuesto de la presente invención y una composición farmacéutica que comprende un fármaco concomitante por separado. La vía de administración del compuesto de la presente invención y la del fármaco concomitante puede ser igual o diferente.

En el caso de una administración combinada, el compuesto de la presente invención se puede administrar una vez por día o varias veces por día en una dosis individual de 0.01 mg a 1 g, o se puede administrar en una dosis menor. El fármaco concomitante se puede administrar en una dosis usada generalmente para la prevención o el tratamiento de una infección por VIH, por ejemplo, en una dosis individual de 0.01 mg a 0.3 g. De modo alternativo, se puede administrar en una dosis menor.

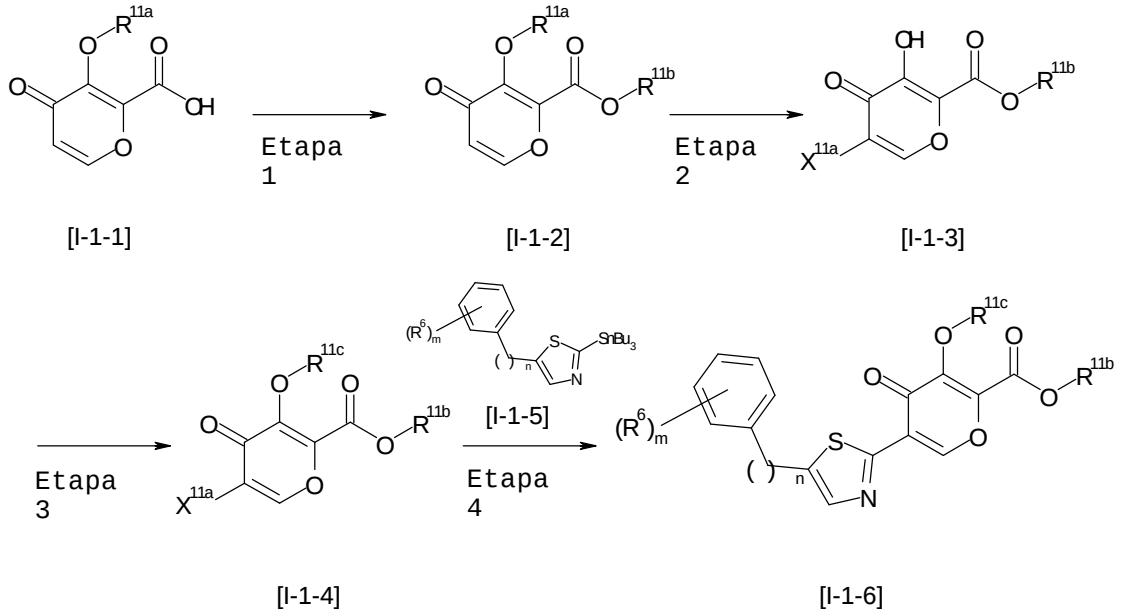
Ahora, se explicarán específicamente los métodos de producción del compuesto de la presente invención. Sin embargo, la presente invención no está limitada a estos métodos de producción. Para la producción del compuesto de la presente invención, el orden de las reacciones se puede cambiar de forma apropiada. Las reacciones se pueden realizar a partir de una etapa razonable o una porción de sustitución razonable. Además, se puede insertar una etapa de conversión de sustituyente apropiada (conversión o modificación adicional del sustituyente) entre las respectivas etapas. Cuando está presente un grupo funcional reactivo, la protección y la desprotección se pueden realizar de forma apropiada. Asimismo, para promover el progreso de las reacciones, se pueden usar reactivos distintos de los ejemplificados más adelante de modo apropiado. Los compuestos de partida cuyos métodos de producción no se describen son asequibles comercialmente o se pueden preparar con facilidad por medio de una combinación de reacciones de síntesis conocidas. El compuesto obtenido en cada etapa se puede purificar por medio de métodos convencionales tales como destilación, recristalización, cromatografía en columna, y similares. En algunos casos, la siguiente etapa se puede llevar a cabo sin aislamiento y purificación.

En los siguientes métodos de producción, la “temperatura ambiente” implica 1 a 40 ºC.

Método de producción I

Método de producción I–1

De los compuestos [I–3–1] en el método de producción I–3 antes mencionado, el compuesto [I–1–6] que es el compuesto [I–3–1] en donde Y es CH, se puede sintetizar por medio del siguiente método.



[I-1-1] [I-1-2] [I-1-3] [I-1-4] [I-1-6]

en donde R^{11a} y R^{11c} son iguales o diferentes y cada uno es un grupo protector de hidroxilo tales como un grupo acetilo, un grupo bencilo, un grupo metilo, un grupo etilo, un grupo isopropilo, un grupo trimetilsililo, un grupo trietilsililo, un grupo ter–butildimetilsililo, un grupo triisopropilsililo, un grupo ter–butildifenilsililo, y similares, R^{11b} es un grupo protector de carboxilo tal como un grupo metilo, un grupo etilo, un grupo bencilo, un

grupo ter–butilo, y similares, X^{11a} es un átomo de halógeno tales como un átomo de cloro, un átomo de bromo, y similares y los demás símbolos son cada uno tal como se describieron con anterioridad.

Etapa 1

El compuesto [I–1–2] se puede obtener introduciendo un grupo protector en el grupo carboxilo de compuesto [I–1–1] de acuerdo con un método conocido.

Por ejemplo, cuando R^{11b} es un grupo metilo, el compuesto [I–1–2] se puede obtener haciendo reaccionar el compuesto [I–1–1] con trimetilsilildiazometano a una baja temperatura hasta temperatura ambiente en un solvente individual o mixto tales como tetrahidrofurano (THF), tolueno, metanol, etanol, y similares.

Etapa 2

El compuesto [I–1–3] se puede obtener introduciendo un átomo de halógeno X^{11a} en el compuesto [I–1–2] de acuerdo con un método conocido.

Por ejemplo, cuando X^{11a} es un átomo de bromo, el compuesto [I–1–3] se puede obtener haciendo reaccionar el compuesto [I–1–2] con un reactivo de bromación (por ejemplo, bromo, tribromuro de trimetilfenilamonio, etc.) a temperatura ambiente bajo calentamiento en un solvente tales como cloroformo, cloruro de metileno, ácido acético, y similares.

Etapa 3

El compuesto [I–1–4] se puede obtener introduciendo un grupo protector en un grupo hidroxilo de compuesto [I–1–3] de acuerdo con un método conocido.

Por ejemplo, cuando R^{11c} es un grupo bencilo, el compuesto [I–1–4] se puede obtener haciendo reaccionar el compuesto [I–1–3] con haluro de bencilo (por ejemplo, cloruro de bencilo, bromuro de bencilo, etc.) a temperatura ambiente bajo calentamiento en presencia de una base tales como acetato de potasio, carbonato de potasio, hidrógeno–carbonato de potasio, hidrógeno–carbonato de sodio, fosfato de potasio, trietilamina, hidrógeno–fosfato de sodio, carbonato de cesio, hidruro de sodio, t–butóxido de potasio, diisopropilamida de litio (LDA), y similares en un solvente tales como N,N–dimetilformamida (DMF), dimetilacetamida (DMA), acetonitrilo, 1,2–dimetoxietano, THF, tolueno, y similares.

Etapa 4

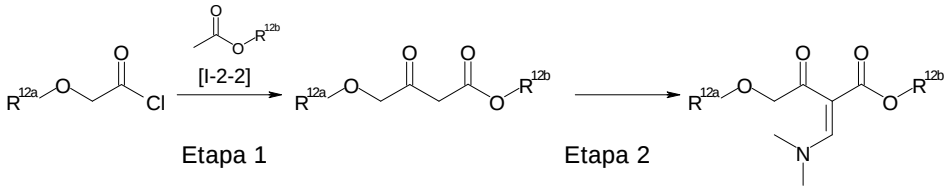
El compuesto [I–1–6] se puede obtener sometiendo el compuesto [I–1–4] a una reacción de acoplamiento con el compuesto [I–1–5] en presencia de un catalizador de paladio (por ejemplo, tris(dibencilidenacetona)dipaladio (0), tetrakis(trifenilfosfina)paladio (0) y dicloruro de bis(trifenilfosfina)paladio (II), etc.) a temperatura ambiente hasta bajo calentamiento en un solvente tales como DMF, DMA, acetonitrilo, tolueno, 1,4–dioxano, y similares. Para el progreso preferible de la reacción, también se puede añadir un ligando (por ejemplo, tri(2–

furil)fosfina, tributilfosfina, etc.).

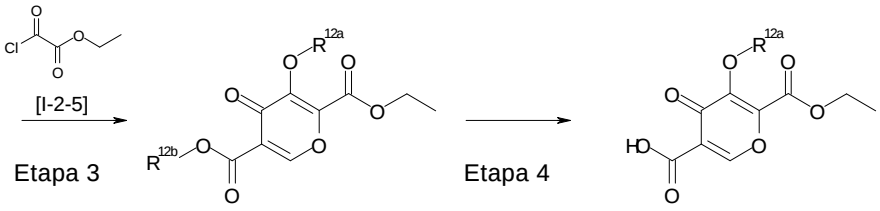
Por ejemplo, el compuesto [I–1–5], en donde n es 1, se puede obtener de la misma manera que en la etapa 1R–2 y la etapa 1R–3 del Ejemplo de referencia 1 mencionado más abajo.

Método de producción I–2

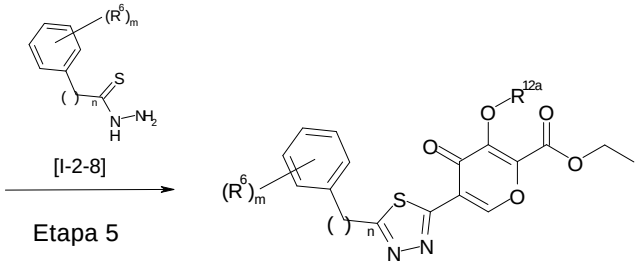
De los compuestos [I–3–1] en el método de producción I–3 mencionado más abajo, el compuesto [I–2–9] que es el compuesto [I–3–1], en donde Y es un átomo de nitrógeno y R^{13b} es un grupo etilo, se puede sintetizar por medio del siguiente método.



[I-2-1] [I-2-3] [I-2-4]



[I-2-6] [I-2-7]



[I-2-9]

en donde R^{12a} es un grupo protector de hidroxilo tales como

grupo acetilo, grupo bencilo, grupo metilo, grupo etilo, grupo isopropilo, grupo trimetilsililo, grupo trietilsililo, grupo ter–butildimetilsililo, grupo triisopropilsililo, grupo ter–butildifenilsililo, y similares, R^{12b} es un grupo protector de carboxilo tales como grupo metilo, grupo etilo, grupo bencilo, ter–butilo, y similares y los demás símbolos son cada uno tal como se describieron con anterioridad.

Etapa 1

El compuesto [I–2–3] se puede obtener haciendo reaccionar el compuesto [I–2–1] con el compuesto [I–2–2] a –78 ºC en condiciones de temperatura ambiente en un solvente tales como DMF, DMA, dimetilsulfóxido (DMSO), THF, tolueno, y similares, en presencia de una base tales como hidruro de sodio, diisopropilamida de litio (LDA), hexametildisilazida de litio (LHMDS), y similares.

Etapa 2

El compuesto [I–2–4] se puede obtener haciendo reaccionar el compuesto [I–2–3] con N,N–dimetilformamida dimetilacetal a temperatura ambiente hasta bajo calentamiento en un solvente tales como DMF, acetonitrilo, THF, cloroformo, acetato de etilo, cloruro de metileno, tolueno, y similares.

Etapa 3

El compuesto [I–2–6] se puede obtener añadiendo una base tales como hidruro de sodio, LDA, LHMDS, y similares a una solución del compuesto [I–2–4] disuelto en un solvente tales como DMF, DMA, DMSO,

THF, tolueno, y similares a –78 ºC hasta temperatura ambiente, haciendo reaccionar el compuesto con el compuesto [I–2–5] y tratándolo con trietilamina, diisopropiletilamina, o similares.

Etapa 4

El compuesto [I–2–7] se puede obtener eliminando el grupo protector de carboxilo R^{12b} del compuesto [I–2–6] por un método conocido. Por ejemplo, cuando el grupo protector es un grupo ter–butilo, el compuesto [I–2–7] se puede obtener agitando el compuesto [I–2–6] a una baja temperatura hasta bajo calentamiento en un solvente individual o mixto de hexano, cloroformo, cloruro de metileno, acetato de etilo, tolueno, 1,2–dimetoxietano, 1,4–dioxano, THF, metanol, etanol, 2–propanol, DMSO, DMF, DMA, acetonitrilo, agua, y similares en presencia de ácido tales como ácido p–toluensulfónico, ácido metansulfónico, trifluoruro de boro, tricloruro de boro, tribromuro de boro, tricloruro de aluminio, ácido clorhídrico, bromuro de hidrógeno, ácido fosfórico, ácido sulfúrico, ácido acético, ácido trifluoroacético, y similares.

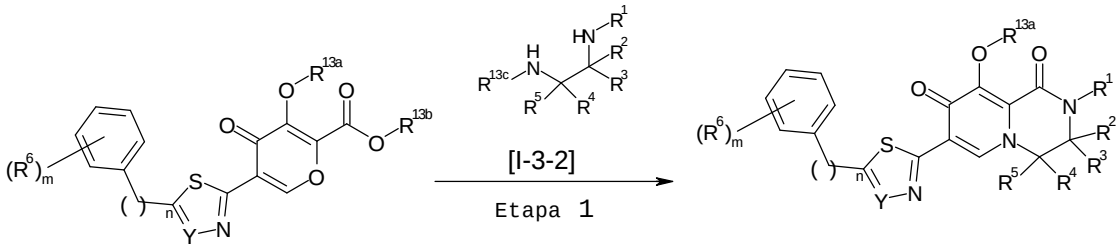
Etapa 5

El compuesto [I–2–9] se puede obtener convirtiendo el compuesto [I–2–7] en cloruro de ácido por un método conocido y luego haciendo reaccionar el compuesto con el compuesto [I–2–8]. Específicamente, el compuesto [I–2–9] se puede obtener convirtiendo el compuesto [I–2–7] en cloruro de ácido con un agente de cloración tales como cloruro de oxalilo, cloruro de tionilo, tricloruro de fósforo, y similares a

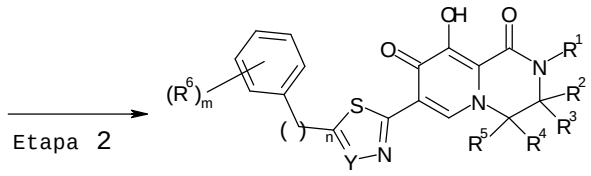
una baja temperatura hasta temperatura ambiente en un solvente individual o mixto de hexano, cloroformo, cloruro de metileno, acetato de etilo, tolueno, 1,2–dimetoxietano, 1,4–dioxano, THF, y similares en presencia de una cantidad catalítica de DMF de ser necesario y haciendo reaccionar el compuesto con el compuesto [I–2–8].

Método de producción I–3

Un compuesto representado por la fórmula [I] antes mencionado se puede sintetizar por medio del siguiente método.



[I-3-1] [I-3-3]



[I]

en donde R^{13a} es un grupo protector de hidroxilo tales como grupo acetilo, grupo bencilo, grupo metilo, grupo etilo, grupo isopropilo, grupo trimetilsililo, grupo trietilsililo, grupo ter–butildimetilsililo, grupo triisopropilsililo, grupo ter–butildifenilsililo, y similares, R^{13b} es un grupo protector de carboxilo

tales como grupo metilo, grupo etilo, grupo bencilo, ter–butilo, y similares, R^{13c} es un grupo protector de amino tales como grupo benciloxicarbonilo, grupo ter–butoxicarbonilo, grupo bencilo, y similares y los demás símbolos son cada uno tal como se describieron con anterioridad.

Etapa 1

El compuesto [I–3–3] se puede obtener haciendo reaccionar el compuesto [I–3–1] con el compuesto [I–3–2], en donde el grupo protector de amino R^{13c} se elimina primero de acuerdo con un método conocido a temperatura ambiente hasta bajo calentamiento en un solvente individual o mixto de cloroformo, diclorometano, DMF, DMA, DMSO, acetonitrilo, 1,2–dimetoxietano, THF, tolueno, agua, y similares y ciclando el compuesto en presencia de una base tales como trietilamina, diisopropilamina, diisopropiletilamina, diazabiciclounde ceno, carbonato de sodio, carbonato de potasio, hidrógeno–carbonato de sodio, y similares. La reacción de ciclación también se puede llevar a cabo en presencia de un ácido tales como ácido acético, ácido p–toluensulfónico, ácido metansulfónico, trifluoruro de boro, tricloruro de boro, tribromuro de boro, ácido clorhídrico, bromuro de hidrógeno, ácido fosfórico, ácido sulfúrico, y similares.

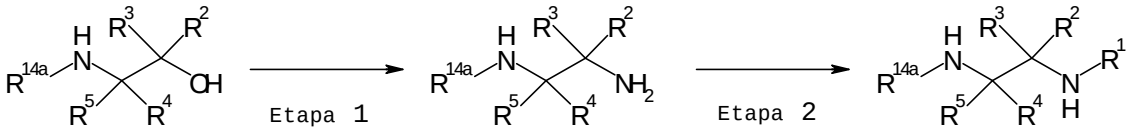
Etapa 2

El compuesto [I] se puede obtener eliminando el grupo protector de hidroxilo R^{13a} del compuesto [I–3–3] por un método conocido. Por ejemplo, cuando el grupo protector es un grupo bencilo, el compuesto [I] se puede obtener agitando el compuesto [I–3–3] a una baja temperatura

hasta temperatura ambiente en un solvente individual o mixto de hexano, cloroformo, cloruro de metileno, acetato de etilo, tolueno, metanol, etanol, 2–propanol, THF, 1,4–dioxano, acetonitrilo, agua, y similares, en presencia de un ácido tales como ácido clorhídrico, ácido sulfúrico, bromuro de hidrógeno, ácido fosfórico, ácido acético, ácido trifluoroacético, y similares. El ácido se puede usar como un solvente.

Método de producción I–4

El compuesto [I–3–2] en el método de producción I–3 antes mencionado (correspondiente al siguiente compuesto [I–4–3]) se puede sintetizar por medio del siguiente método.



[I-4-1] [I-4-2] [I-4-3]

en donde R^{14a} es un grupo protector de amino tales como grupo benciloxicarbonilo, grupo ter–butoxicarbonilo, bencilo, y similares y los demás símbolos son cada uno tal como se describieron con anterioridad.

Etapa 1

El compuesto [I–4–1] que se puede obtener de un compuesto disponible comercialmente por un método conocido se hace reaccionar con ftalimida a una baja temperatura a bajo calentamiento en un solvente individual o mixto de THF, cloruro de metileno, cloroformo, DMF, acetato de

etilo, tolueno, y similares en presencia de un reactivo de fósforo tales como trifenilfosfina, difenil(2–piridil)fosfina, tributilfosfina, tri–ter–butilfosfina, y similares y un compuesto azoico tales como diisopropilazodicarboxilato, dietilazodicarboxilato, N,N,N',N'–tetrametilazodicarboxamida, 1,1'–(azodicarbonil)dipiperidina, y similares y el compuesto obtenido se trata luego con hidrazina para eliminar un grupo ftaloílo para dar el compuesto de amina [I–4–2].

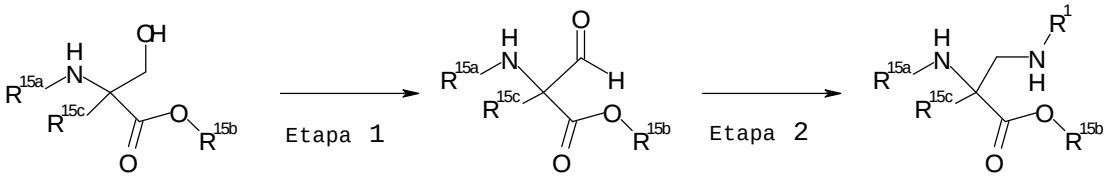
Etapa 2

El compuesto [I–4–2] se hace reaccionar con un compuesto de cetona o compuesto de aldehído a una baja temperatura hasta temperatura ambiente en un solvente tales como DMF, acetonitrilo, THF, cloroformo, acetato de etilo, cloruro de metileno, tolueno, y similares y la mezcla se agita en presencia de un agente de reducción tales como borhidruro de sodio, triacetoxiborhidruro de sodio, y similares para introducir el sustituyente R^1 en el grupo amino del compuesto [I–4–2], pudiendo obtener el compuesto [I–4–3].

Método de producción I–5

De los compuestos [I–3–2] en el método de producción I–3 antes mencionado, un compuesto, que es el compuesto [I–3–2] en donde en particular R^2 y R^3 son cada uno un átomo de hidrógeno, uno de R^4 y R^5 es un grupo carboxilo o $–CO–NR^aR^b$, en donde R^a y R^b son como se describió con anterioridad y el otro es un grupo alquilo de $C_{1–6}$

opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo A antes mencionado, se puede sintetizar por medio del siguiente método.



[I-5-1] [I-5-2] [I-5-3]

en donde R^{15a} es un grupo protector de amino tales como grupo benciloxicarbonilo, grupo ter–butoxicarbonilo, bencilo, y similares, R^{15b} es un grupo protector de carboxilo tales como grupo metilo, grupo etilo, grupo bencilo, grupo ter–butilo, y similares, R^{15c} es un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo A antes mencionado y los demás símbolos son cada uno tal como se describieron con anterioridad.

Etapa 1

El compuesto [I–5–2] se puede obtener oxidando el grupo hidroxilo del compuesto [I–5–1] que se puede obtener de un compuesto disponible comercialmente por un método conocido, en un grupo aldehído por un complejo de óxido de cromo–piridina (por ejemplo, clorocromato de piridinio, dicromato de piridinio, y similares), un oxidante de metal (por ejemplo, óxido de cromo, carbonato de plata, dióxido de manganeso, y similares), por oxidación de DMSO usando diversos activadores de DMSO tales como cloruro de oxalilo, anhídrido trifluoroacético, anhídrido acético,

diciclohexilcarbodiimida (DCC), complejo de trióxido de azufre–piridina, y similares, oxidación de Dess–Martin, y similares de acuerdo con un método conocido.

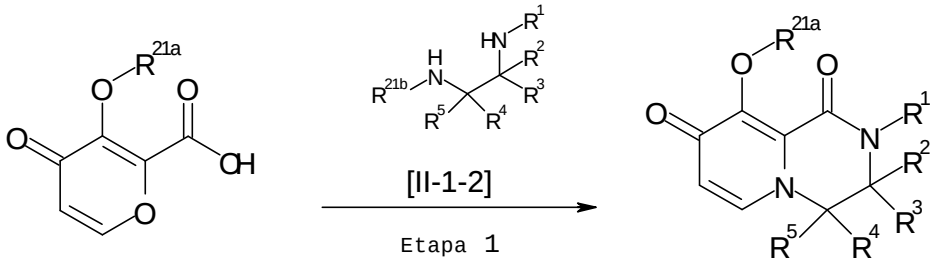
Etapa 2

El compuesto [I–5–3] se puede obtener sometiendo el grupo aldehído del compuesto [I–5–2] a una aminación reductiva en condiciones similares a las del Método de producción I–4, etapa 2. El compuesto obtenido [I–5–3] se cicla por el método antes mencionado y el grupo protector de carboxilo R^{15b} se elimina por un método conocido y, de ser necesario, el compuesto resultante se hace reaccionar con un compuesto de amina por un método conocido para dar el compuesto objeto.

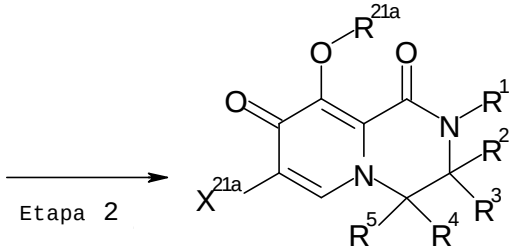
Método de producción II

Método de producción II–1

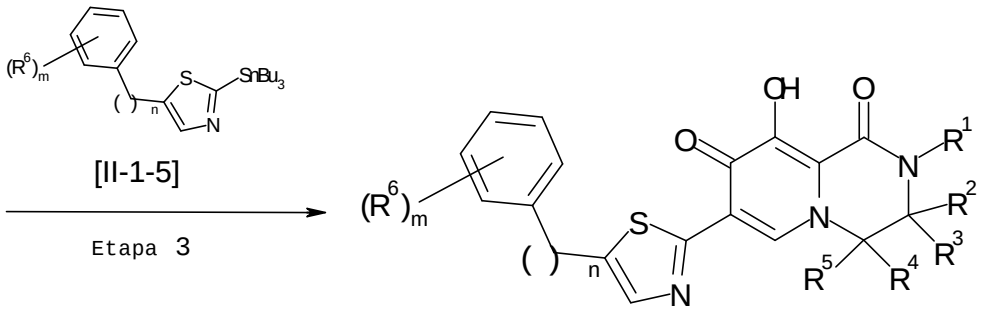
De los compuestos representados por la fórmula [I] antes mencionada, el compuesto [II–1–6], que es el compuesto [I] en donde Y es CH se puede sintetizar por medio del siguiente método.



[II-1-1] [II-1-2] Etapa 1 [II-1-3]



Etapa 2 [II-1-4]



[II-1-5] Etapa 3 [II-1-6]

en donde R^{21a} es un grupo protector de hidroxilo tales como grupo acetilo, grupo bencilo, grupo metilo, grupo etilo, grupo isopropilo, grupo trimetilsililo, grupo trietilsililo, grupo ter–butildimetilsililo, grupo triisopropilsililo, grupo ter–butildifenilsililo, y similares, R^{21b} es un grupo protector de amino tales como grupo benciloxicarbonilo, grupo ter–butoxicarbonilo, grupo bencilo, y

similares, X^{21a} es un grupo saliente tales como un átomo de halógeno (por ejemplo, átomo de flúor, átomo de cloro, átomo de bromo, átomo de yodo, y similares), grupo p–toluensulfoniloxi (OTs), grupo metansulfoniloxi (OMs), grupo trifluorometansulfoniloxi (OTf), y similares y los demás símbolos son cada uno tal como se describieron con anterioridad.

Etapa 1

El compuesto [II–1–3] se puede obtener convirtiendo el compuesto [II–1–1] en cloruro de ácido por un método conocido a una baja temperatura bajo calentamiento, haciendo reaccionar el cloruro de ácido con el compuesto [II–1–2], eliminando el grupo protector de amino R^{21b} y agitando la mezcla en presencia de una base tales como acetato de potasio, carbonato de potasio, hidrógeno–carbonato de potasio, hidrógeno–carbonato de sodio, fosfato de potasio, trietilamina, diisopropiletilamina, hidrógeno–fosfato de sodio, carbonato de cesio, y similares.

El compuesto [II–1–2] se puede obtener por un método similar al del Método de producción I–4.

Etapa 2

El compuesto [II–1–4] se puede obtener introduciendo un grupo saliente X^{21a} en el compuesto [II–1–3] por un método conocido.

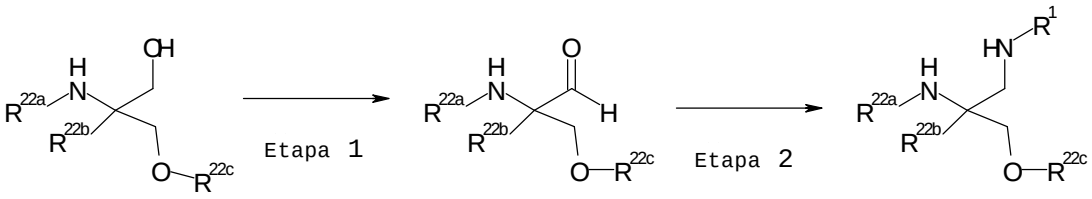
Por ejemplo, cuando el grupo saliente X^{21a} es un átomo de bromo, el átomo de bromo se introduce en el compuesto [II–1–3] por medio de un método similar al del Método de producción I–1, etapa 2 para dar el compuesto [II–1–4].

Etapa 3

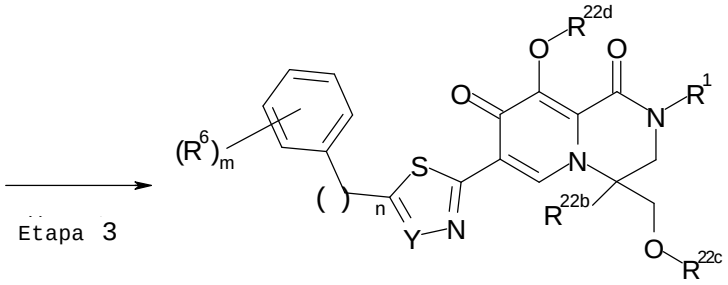
El compuesto [II–1–4] se hace reaccionar con el compuesto [II–1–5] por un método similar al del Método de producción I–1, etapa 4 y el grupo protector de hidroxilo R^{21a} se elimina por un método similar al del Método de producción I–3, etapa 2, pudiendo obtener el compuesto [II–1–6].

Método de producción II–2

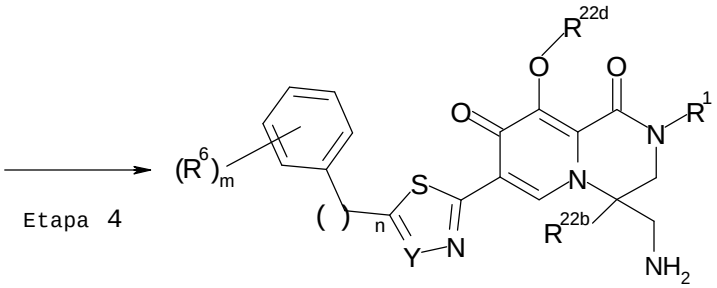
De los compuestos representados por la fórmula [I] antes mencionada, un compuesto, que es el compuesto [I] en donde en particular R^2 y R^3 son cada uno un átomo de hidrógeno y uno de R^4 y R^5 es un grupo metilo sustituido con $–NR^{A3}R^{A4}$, en donde R^{A3} y ^{A4} son como se describió con anterioridad y el otro es un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo A antes mencionado, se puede sintetizar por medio del siguiente método.



[II-2-1] [II-2-2] [II-2-3]



[II-2-4]



[II-2-5]

en donde R^{22a} es un grupo protector de amino tales como grupo benciloxicarbonilo, grupo ter–butoxicarbonilo, bencilo, y similares, R^{22b} es un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del grupo A antes mencionado, R^{22c} y R^{22d} son iguales o diferentes y cada uno es un grupo protector de hidroxilo tales como grupo acetilo, grupo bencilo, grupo metilo, grupo etilo, grupo isopropilo, grupo trimetilsililo, grupo trietilsililo, grupo ter–butildimetilsililo, grupo triisopropilsililo, grupo ter–butildifenilsililo, y similares y los demás

símbolos son cada uno tal como se describieron con anterioridad.

Etapa 1

El grupo hidroxilo de compuesto [II–2–1] se oxida, por un método conocido para dar el grupo aldehído, pudiendo obtener el compuesto [II–2–2]. El método conocido es el mismo que el indicado, por ejemplo, para el Método de producción I–5, etapa 1.

Etapa 2

El compuesto [II–2–3] se puede obtener sometiendo el compuesto [II–2–2] por aminación reductiva por medio del mismo método que el Método de producción I–5, etapa 2.

Etapa 3

El compuesto [II–2–4] se puede obtener del compuesto [II–2–3] por medio del mismo método que el Método de producción II–1, etapa 1 a etapa 3.

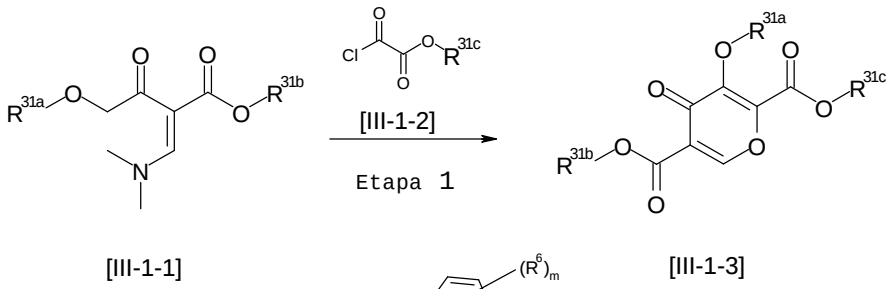
Etapa 4

El grupo protector de hidroxilo R^{22c} del compuesto [II–2–4] se elimina por un método conocido y el grupo hidroxilo se somete apropiadamente a la conversión del sustituyente a un grupo saliente (OTs, OMs, OTf etc.). Después de la reacción con ftalimida de potasio y el grupo ftaloílo se elimina por medio de un método similar al Método de producción I–4, etapa 1 para dar el compuesto [II–2–5]. El compuesto obtenido [II–2–5] se somete a una combinación apropiada de eliminación del grupo protector de hidroxilo R^{22d} por medio de un método similar al Método de producción

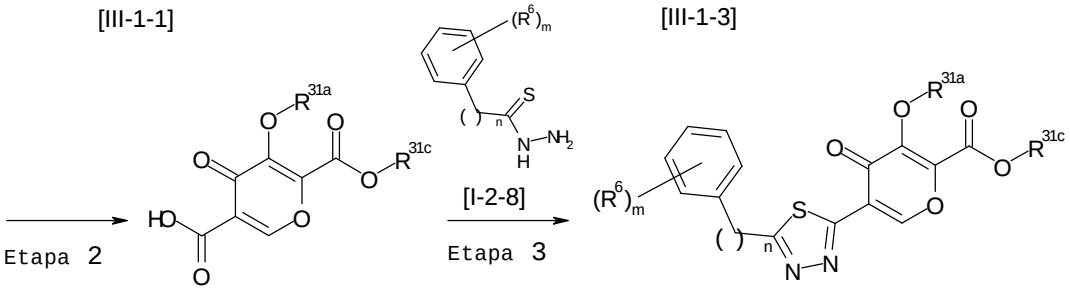
I–3, etapa 2 y modificación del grupo amino del compuesto [II–2–5] por un método conocido para dar el compuesto objeto.

Método de producción III

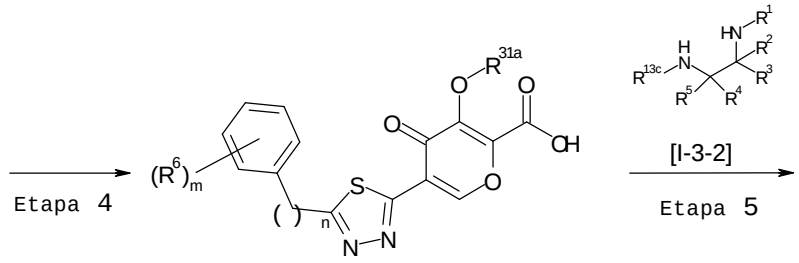
De los compuestos representados por la fórmula [I] antes mencionada, el compuesto [III–1–9], que es el compuesto [I], en donde Y es un átomo de nitrógeno, se puede sintetizar por medio del siguiente método.



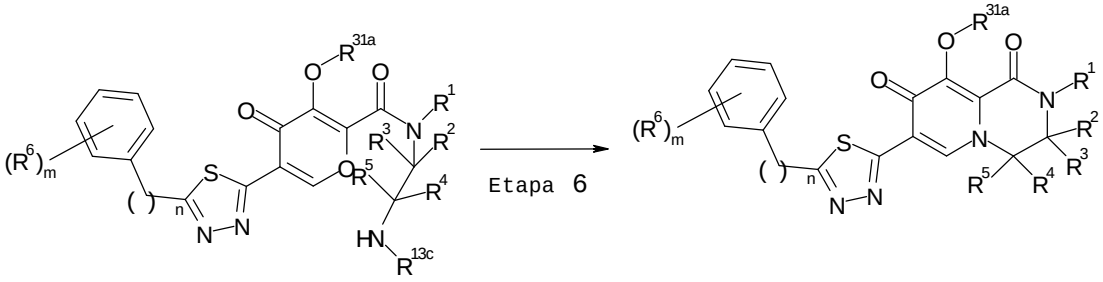
[III-1-1] [III-1-3]



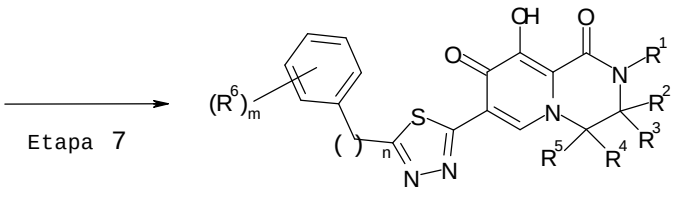
[III-1-4] [III-1-5]



[III-1-6]



[III-1-7] [III-1-8]



[III-1-9]

en donde R^{31a} es un grupo protector de hidroxilo tales como grupo acetilo, grupo bencilo, grupo metilo, grupo etilo, grupo isopropilo, grupo trimetilsililo, grupo trietilsililo, grupo ter–butildimetilsililo, grupo triisopropilsililo, grupo ter–butildifenilsililo, y similares, R^{31b} y R^{31c} son iguales o diferentes y cada uno es un grupo protector de carboxilo tales como grupo metilo, grupo etilo, grupo bencilo, grupo ter–butilo, y similares y los demás símbolos son cada uno tal como se describieron con anterioridad.

Etapa 1

El compuesto [III–1–3] se puede obtener haciendo reaccionar el compuesto [III–1–1] con el compuesto [III–1–2] por medio de un método similar al Método de producción I–2, etapa 3.

Etapa 2

El compuesto [III–1–4] se puede obtener eliminando el grupo protector de carboxilo R^{31b} del compuesto [III–1–3] por medio de un método similar al Método de producción I–2, etapa 4.

Etapa 3

El compuesto [III–1–5] se puede obtener haciendo reaccionar el compuesto [III–1–4] con el compuesto [I–2–8] por medio de un método similar al Método de producción I–2, etapa 5.

Etapa 4

El compuesto [III–1–6] se puede obtener eliminando el grupo protector de carboxilo R^{31c} del compuesto [III–1–5] por un método conocido.

Etapa 5

El compuesto [III–1–7] se puede obtener convirtiendo el compuesto [III–1–6] en cloruro de ácido por medio de un método similar al Método de producción I–2, etapa 5 y haciendo reaccionar el cloruro de ácido con el compuesto [I–3–2] en un solvente tales como hexano, cloroformo, cloruro de metileno, acetato de etilo, tolueno, 1,2–dimetoxietano, 1,4–dioxano, THF, y similares en presencia de una base tales como acetato de potasio, carbonato de potasio, hidrógeno–carbonato de potasio, hidrógeno–carbonato de sodio, fosfato de potasio, trietilamina, diisopropiletilamina, hidrógeno–fosfato de sodio, carbonato de cesio, y similares.

Etapa 6

El compuesto [III–1–8] se puede obtener eliminando el grupo protector de amino R^{13c} del compuesto [III–1–7] por un método conocido y realizando la ciclación por medio de un método similar a una reacción de ciclación del Método de producción II–1, etapa 1 en presencia de una base.

Etapa 7

El compuesto [III–1–9] se puede obtener eliminando el grupo protector de hidroxilo R^{31a} del compuesto [III–1–8] por un método conocido. Por ejemplo, cuando el grupo protector es un grupo bencilo, se puede usar un método similar al Método de producción I–3, etapa 2.

EJEMPLOS

Ahora, los métodos de producción del compuesto de la presente invención se explican específicamente haciendo referencia a los Ejemplos, que no se construyeron para ser limitativos.

Las abreviaturas usadas en los Ejemplos significan lo siguiente.

Bn: grupo bencilo

Boc: grupo ter–butoxicarbonilo

Et: grupo etilo

Me: grupo metilo

Ms: grupo metansulfonilo

TBS: grupo ter–butildimetilsililo

TFA: ácido trifluoroacético

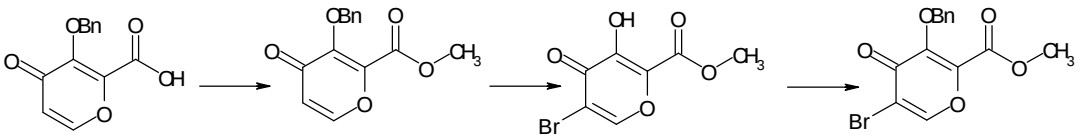
THP: grupo tetrahidropiranilo

Z: grupo benciloxicarbonilo

Además, los siguientes valores de ^{1}H–NMR se midieron por resolución a 400 MHz.

EJEMPLO DE REFERENCIA 1

Etapa 1R–1

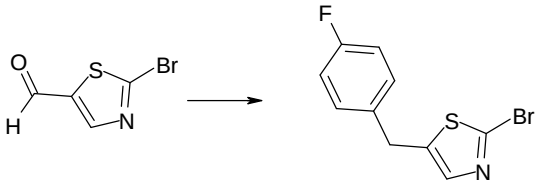


El ácido 3–benciloxi–4–oxo–4H–piran–2–carboxílico (11.43 g) se suspendió en metanol (20 ml)–tetrahidrofurano (80 ml), se añadió solución 2 M de (trimetilsilil)diazometano/hexano (46.4 ml) gota a gota bajo enfriamiento con hielo y la mezcla se agitó a temperatura ambiente durante 1.5 h. El solvente se evaporó a presión reducida y el residuo obtenido se disolvió en cloroformo (80 ml). A ello se añadió bromo (23 ml) y la mezcla se agitó durante 2 días a 75 ºC. La mezcla se dejó enfriar hasta temperatura ambiente, se añadió hexano y el sólido precipitado se recogió por filtración. El sólido obtenido se disolvió en dimetilformamida (54 ml), se añadieron carbonato de potasio (7.1 g) y bromuro de bencilo (5.6 ml) y la mezcla se agitó a 80 ºC durante 40 min. La mezcla se dejó enfriar hasta temperatura ambiente y se filtró. El filtrado se concentró y se añadió solución acuosa 1 N de ácido clorhídrico al residuo obtenido. La mezcla se extrajo dos veces con acetato de etilo. La capa combinada de acetato de etilo se lavó con salmuera saturada, se secó y se concentró. El concentrado se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:20 – 1:4), el eluato se concentró y los cristales precipitados se recolectaron por filtración para dar el compuesto objeto

(7.65 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 8.11 (s, 1H), 7.49–7.44 (m, 2H), 7.40–7.32 (m, 3H), 5.32 (s, 2H), 3.89 (s, 3H).

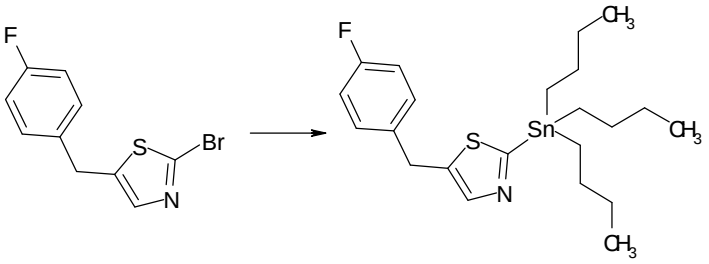
Etapa 1R–2



A una solución de 2–bromotiazol–5–carbaldehído (14 g) en THF (300 ml) se añadió gota a gota solución 1 M de bromuro de (4–fluorofenil)magnesio/THF (80 ml) a –78 ºC y la mezcla se agitó durante 1 h. Se añadió solución acuosa saturada de cloruro de amonio y la mezcla se dejó enfriar hasta temperatura ambiente y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó y se concentró. Se añadieron ácido trifluoroacético (100 ml) y trietilsilano (58 ml) al residuo obtenido y la mezcla se agitó durante 100 min a 75 ºC. La mezcla se dejó enfriar hasta temperatura ambiente y se concentró y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:50 – 1:9) para dar el compuesto objeto (16.8 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 7.31–7.29 (m, 1H), 7.21–7.14 (m, 2H), 7.05–6.98 (m, 2H), 4.07 (s, 2H).

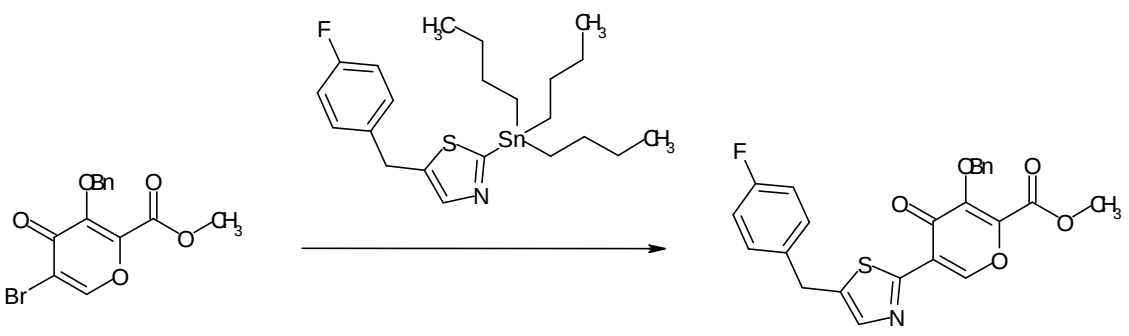
Etapa 1R–3



A una solución del compuesto (3.2 g) obtenida en la etapa 1R–2 en THF (50 ml) se añadió gota a gota solución 1.6 M de n–butil–litio/hexano (8.1 ml) a –78 ºC y la mezcla se agitó durante 10 min. El cloruro de tributilestaño (3.5 ml) se añadió y la mezcla se agitó a –78 ºC durante 30 min y a temperatura ambiente durante 30 min. Se añadió agua helada y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó y se concentró para dar el compuesto objeto (6.2 g) descrito en el esquema antes mencionado en forma de producto crudo.

^{1}H–NMR (THF) δ: 7.76–7.74 (m, 1H), 7.25–7.21 (m, 2H), 7.03–6.97 (m, 2H), 4.19 (s, 2H), 1.65–1.56 (m, 6H), 1.40–1.28 (m, 6H), 1.20–1.13 (m, 6H), 0.91–0.85 (m, 9H).

Etapa 1R–4

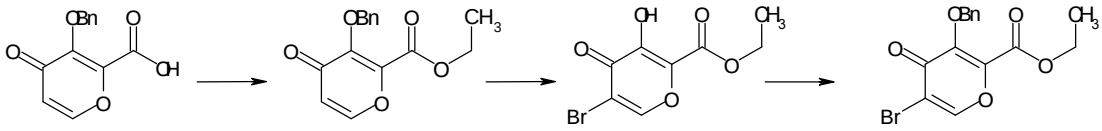


Bajo una corriente de argón, se suspendieron tris(dibencilidenacetona)dipaladio (0) (84 mg) y tri(2–furil)fosfina (85 mg) en tolueno (1.5 ml) y la suspensión se agitó a temperatura ambiente durante 15 min. El compuesto (890 mg) obtenido en la etapa 1R–3 y el compuesto (310 mg) obtenido en la etapa 1R–1 se añadieron y la mezcla se agitó a 80 ºC durante 1 h. La mezcla de reacción obtenida se filtró a través de celite y se concentró y el concentrado se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:20 – 1:4) para dar el compuesto objeto (190 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 8.91 (s, 1H), 7.62–7.61 (m, 1H), 7.51–7.45 (m, 2H), 7.40–7.32 (m, 3H), 7.25–7.19 (m, 2H), 7.04–6.97 (m, 2H), 5.37 (s, 2H), 4.19 (s, 2H), 3.91 (s, 3H).

EJEMPLO DE REFERENCIA 2

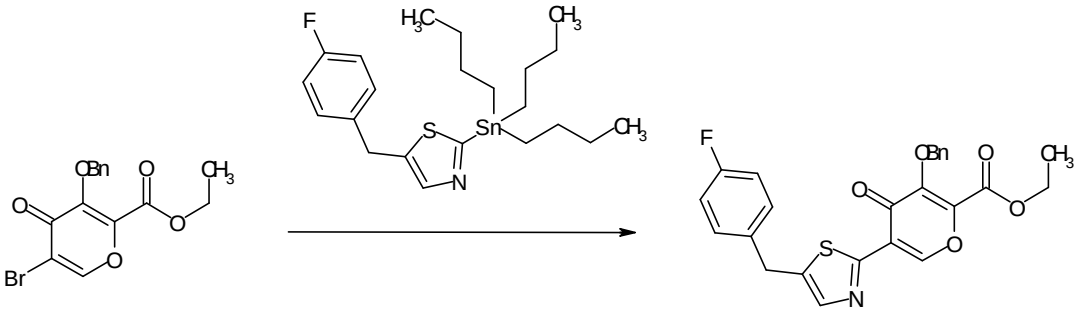
Etapa 2R–1



De la misma manera que en la etapa 1R–1 excepto en que se etiló el ácido 3–benciloxi–4–oxo–4H–piran–2–carboxílico (15.0 g) con yodoetano, se obtuvo el compuesto objeto (10.97 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 8.11 (s, 1H), 7.50–7.46 (m, 2H), 7.40–7.32 (m, 3H), 5.31 (s, 2H), 4.36 (q, 2H, J = 7.2 Hz), 1.33 (t, 3H, J = 7.2 Hz).

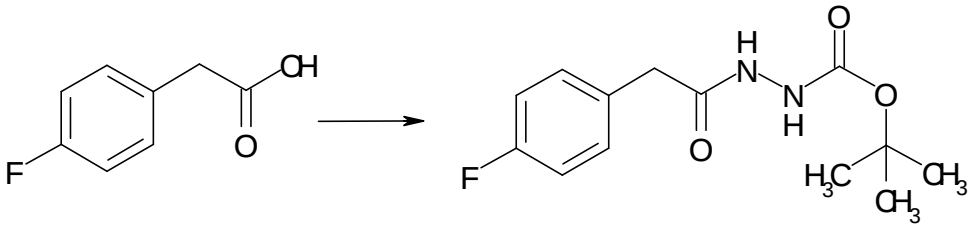
Etapa 2R–2



De la misma manera que en la etapa 1R–4, se obtuvo el compuesto objeto (1.0 g) descrito en el esquema antes mencionado a partir del compuesto (1.2 g) obtenido en la etapa 2R–1.

^{1}H–NMR ($CDCl_3$) δ: 8.91 (s, 1H), 7.62–7.61 (m, 1H), 7.51–7.47 (m, 2H), 7.39–7.31 (m, 3H), 7.25–7.20 (m, 2H), 7.04–6.97 (m, 2H), 5.37 (s, 2H), 4.38 (q, 2H, J = 7.2 Hz), 4.19 (s, 2H), 1.34 (t, 3H, J = 7.2 Hz).

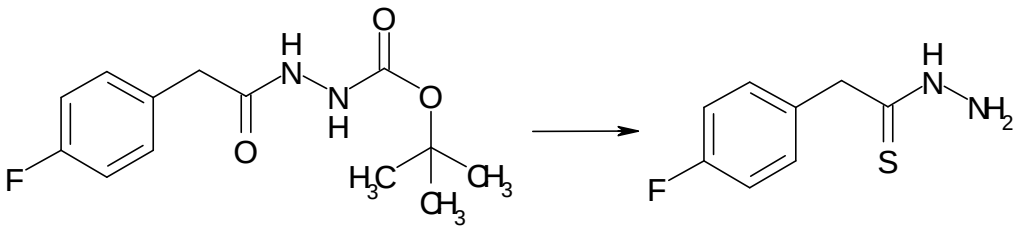
EJEMPLO DE REFERENCIA 3



Etapa 3R–1

A una solución de ácido 4–fluorofenilacético (25 g) y carbazato de ter–butilo (22.5 g) en DMF (200 ml) se añadieron hidrato de 1–hidroxibenzotriazol (HOBT·H2O (27.3 g)) y clorhidrato de 1–etil–3-(3-dimetilaminopropil)carbodiimida (WSC·HCl (34.1 g)) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió solución saturada acuosa de hidrógeno–carbonato de sodio y la mezcla se agitó durante un momento y se extrajo con acetato de etilo. La capa orgánica se lavó con solución saturada acuosa de hidrógeno–carbonato de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró para dar el compuesto objeto (32.3 g) descrito en el esquema antes mencionado en forma de producto crudo.

Etapa 3R–2



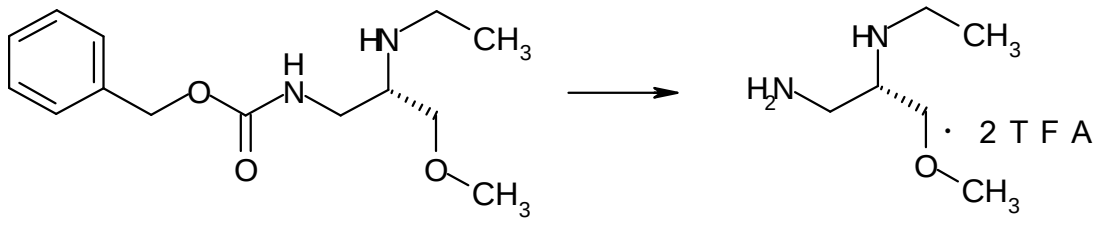
A una solución del compuesto (32.3 g) obtenida en la etapa 3R–1 en THF (300 ml) se añadió un reactivo de Lawesson (48.7 g) y la mezcla se agitó a 50 ºC durante la noche y se dejó enfriar. La mezcla de reacción se vertió en una solución saturada acuosa agitada de hidrógeno–

carbonato de sodio en pequeñas porciones y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla se extrajo dos veces con acetato de etilo y la capa orgánica se lavó con solución saturada acuosa de hidrógeno–carbonato de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró. Al residuo se añadió solución 4 N de ácido clorhídrico/dioxano (300 ml) y la mezcla se agitó a temperatura ambiente durante 1 h. La sal precipitada se recogió por filtración y se disolvió en agua (200 ml) y la solución se neutralizó con hidrógeno–carbonato de sodio y se extrajo dos veces con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de sodio y se concentró. Al residuo se añadió solución de acetato de etilo/hexano (1:4) y la mezcla se lavó en suspensión. El residuo se recogió por filtración y se secó para dar el compuesto objeto (15.78 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 8.27–8.03 (br m, 1H), 7.26–7.20 (m, 2H), 7.10–7.03 (m, 2H), 4.88–4.75 (br m, 2H), 4.08 (s, 2H).

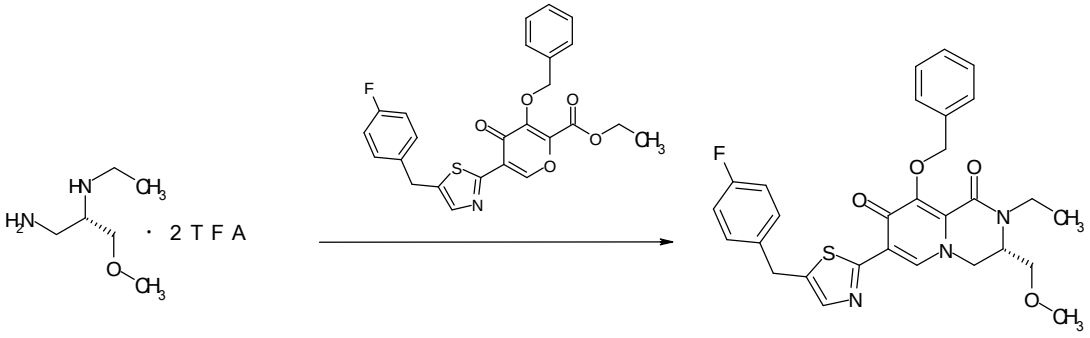
EJEMPLO 1

Etapa 1—1



A una solución de éster bencílico del ácido (S)–2–etilamino–3–metoxipropilcarbámico (76 mg) en metanol (10 ml) se añadió un catalizador de paladio–carbón al 7.5% (100 mg) y la mezcla de reacción se agitó a presión moderada (0.4 MPa) en una atmósfera de hidrógeno a temperatura ambiente durante 3 h. La mezcla de reacción se filtró a través de celite, se añadió ácido trifluoroacético (1 ml) y la mezcla se concentró para dar el compuesto objeto (133 mg) descrito en el esquema antes mencionado en forma de producto crudo.

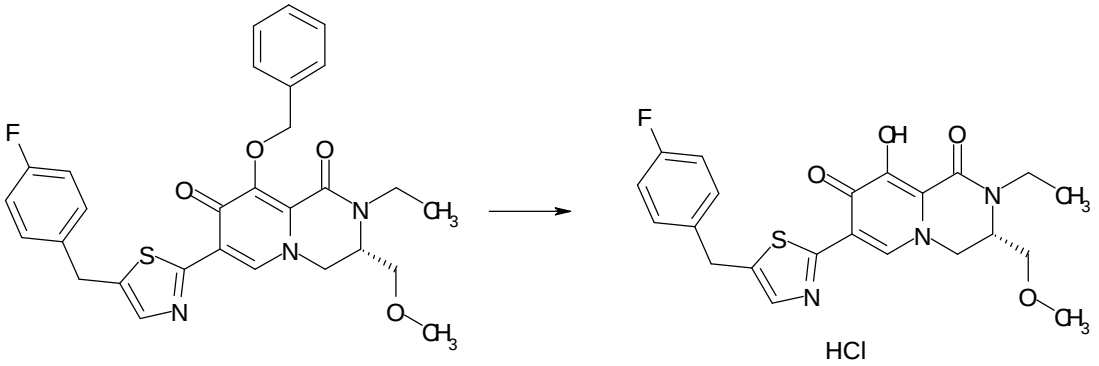
Etapa 1–2



A una solución del compuesto (55 mg) obtenida en la etapa 1–1 en tetrahidrofurano (1.5 ml) se añadió diisopropiletilamina (160 μL) y la mezcla se agitó durante 10 min. Una solución del compuesto (46 mg) obtenida en el Ejemplo de referencia 2 en tetrahidrofurano (1 ml) se añadió y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se concentró, se añadieron tolueno (4 ml) y 1,8–diazabiciclo[5,4,0]undec–7–eno (200 μL) y la mezcla se agitó a 110 ºC durante 15 min. El ácido acético (500 μL) se añadió y la mezcla se agitó a

110 ºC durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y se diluyó con acetato de etilo. La mezcla se lavó con solución acuosa al 5% de hidrógeno–sulfato de potasio, se secó y se concentró y el concentrado se purificó por cromatografía en capa fina de gel de sílice (acetato de etilo:metanol = 20:1) para dar el compuesto objeto (56 mg) descrito en el esquema antes mencionado.

Etapa 1–3



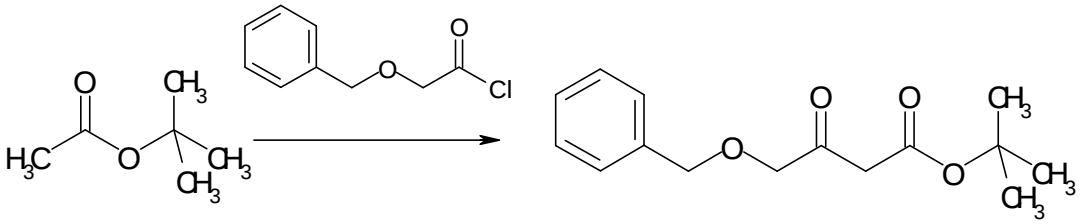
El compuesto (56 mg) obtenido en la etapa 1–2 se disolvió en ácido trifluoroacético (1.0 ml) y la mezcla se dejó reposar a temperatura ambiente durante 1 h. La solución de reacción se concentró, se añadió acetato de etilo y la mezcla se concentró. Acetato de etilo, solución 4 N de ácido clorhídrico/acetato de etilo y hexano se añadieron para permitir la cristalización para dar el compuesto objeto (28 mg) descrito en el esquema antes mencionado.

^{1}H–NMR (DMSO–d_6) δ: 12.30 (br s, 1H), 8.64 (s, 1H), 7.66 (s, 1H), 7.34–7.30 (m, 2H), 7.16–7.11 (m, 2H), 4.57 (d, 1H, J=13.5 Hz), 4.39 (dd, 1H,

J=13.5, 3.9 Hz), 4.19 (s, 2H), 4.12–4.10 (m 1H), 3.87–3.80 (m, 1H), 3.53–3.44 (m, 2H), 3.27–3.22 (m, 1H), 3.20 (s, 3H), 1.18 (t, 3H, J=7.1 Hz).

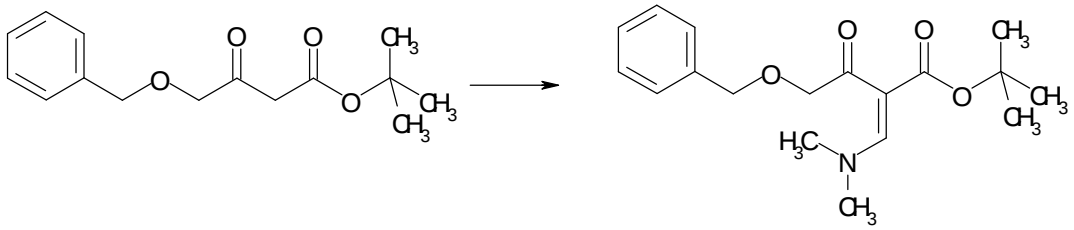
EJEMPLO 2

Etapa 2–1



Bajo nitrógeno, se enfrió una solución 1M de bis(trimetilsilil)amida de litio–THF/etilbenceno (100 ml) en THF (100 ml) hasta –70 ºC y acetato de ter–butilo (13.5 ml) se añadió gota a gota bajo agitación. Después de agitar durante 15 min, el cloruro de benciloxiacetilo (7.52 ml) se añadió gota a gota. Después de agitar durante 1 h, una solución 2 N acuosa de ácido clorhídrico se añadió a la mezcla de reacción hasta alcanzar su pH de 3 y la mezcla se dejó calentar hasta temperatura ambiente. La mezcla se extrajo con acetato de etilo y la capa orgánica se lavó con una solución 2N acuosa de ácido clorhídrico y salmuera saturada, se secó sobre sulfato de sodio y se concentró. La operación anterior se repitió y ambas se combinaron para dar el compuesto objeto (40.3 g) descrito en el esquema antes mencionado en forma de producto crudo.

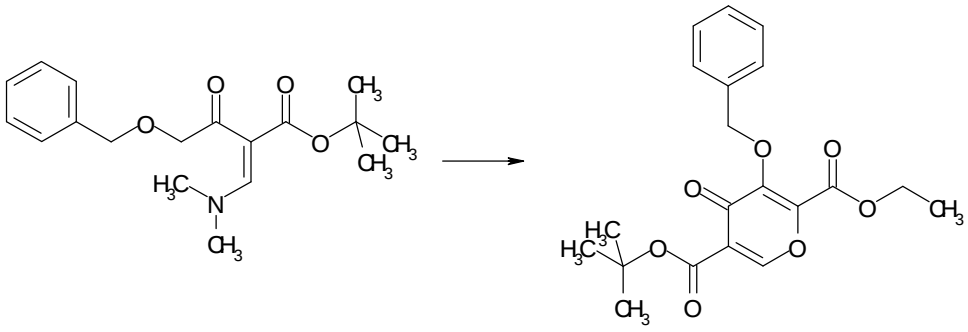
Etapa 2–2



A una solución del compuesto (38 g) obtenido en la etapa 2–1 en tolueno (80 ml) se añadió dimetilformamida dimetilacetal (38 ml) y la mezcla se agitó a 100 ºC durante 1 h. La mezcla se dejó enfriar y se concentró y el concentrado se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2 – acetato de etilo) para dar el compuesto objeto (11.3 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 7.66 (s, 1H), 7.40–7.13 (m, 5H), 4.60 (s, 2H), 4.42 (s, 2H), 3.40–2.65 (m, 6H), 1.45 (s, 9H).

Etapa 2–3

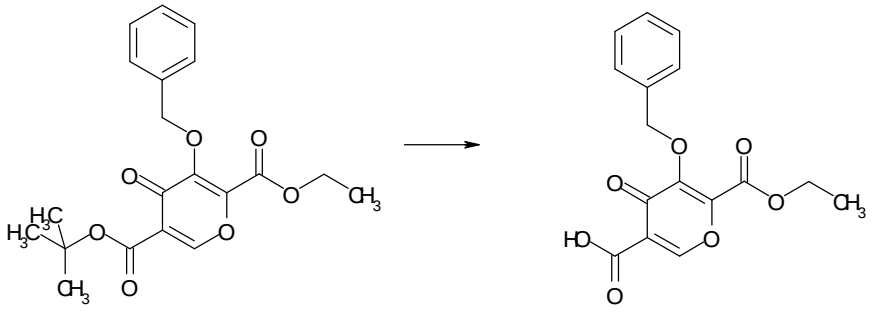


Bajo nitrógeno, una solución 1M de bis(trimetilsilil)amida de litio–THF/etilbenceno (42.5 ml) en THF (150 ml) se enfrió hasta –70 ºC y una solución del compuesto (11.3 g) obtenida en la etapa 2–2 en THF (50

ml) se añadió gota a gota durante 3 min bajo agitación. Después de agitar durante 20 min, el cloroglioxilato de etilo (4.75 ml) se añadió de una vez. Después de agitar durante 25 min, solución saturada acuosa de hidrógeno–sulfato de potasio y acetato de etilo se añadieron y la mezcla se dejó calentar hasta temperatura ambiente. La capa orgánica se separó, se lavó con salmuera saturada, se secó sobre sulfato de sodio y se concentró. Tolueno se añadió al residuo y la mezcla se concentró una vez. Tolueno (100 ml) y trietilamina (10 ml) se añadieron y la mezcla se agitó a temperatura ambiente. Una hora más tarde, la mezcla se concentró y el concentrado se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:6 – 1:3) para dar el compuesto objeto (6.03 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 8.39 (s, 1H), 7.51–7.47 (m, 2H), 7.39–7.30 (m, 3H), 5.32 (s, 2H), 4.34 (q, 2H, J = 7.2 Hz), 1.57 (s, 9H), 1.31 (t, 3H, J = 7.2 Hz).

Etapa 2–4

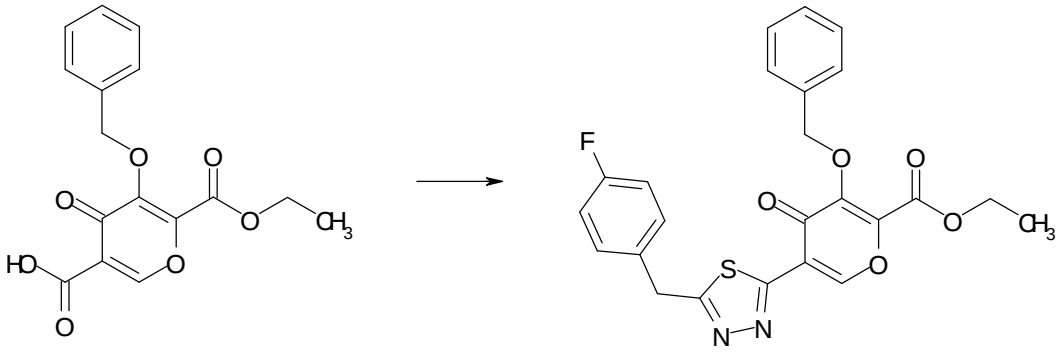


A una solución del compuesto (18.7 g) obtenida en la etapa 2–

3 en acetato de etilo (20 ml) se añadió ácido clorhídrico/acetato de etilo 4N (200 ml) bajo agitación y la mezcla se agitó a temperatura ambiente durante 1 h. A la mezcla de reacción se añadió hexano (1 l), la mezcla se agitó durante un momento y los cristales se recolectaron por filtración y se secaron para dar el compuesto objeto (11.1 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 13.03 (s, 1H), 8.80 (s, 1H), 7.47–7.43 (m, 2H), 7.41–7.35 (m, 3H), 5.38 (s, 2H), 4.40 (q, 2H, J = 7.2 Hz), 1.35 (t, 3H, J = 7.2 Hz).

Etapa 2–5

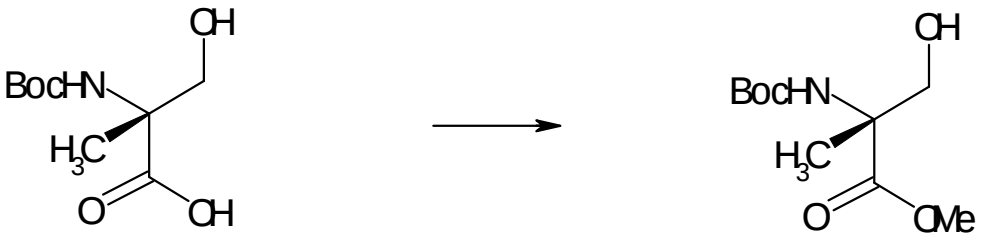


A una solución del compuesto (6 g) obtenida en la etapa 2–4 en tolueno (80 ml) se añadieron cloruro de oxalilo (3.27 ml) y dimetilformamida (0.04 ml) bajo agitación y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró, cloroformo (100 ml) y el compuesto (5.22 g) obtenido en el Ejemplo de referencia 3 se añadieron y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió una solución acuosa al 5% de hidrógeno–

sulfato de potasio y la mezcla se extrajo dos veces con cloroformo. La capa orgánica se lavó con una solución acuosa al 5% de hidrógeno–sulfato de potasio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró. El concentrado se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4 – 1:3), una solución de acetato de etilo/hexano (1:3) se añadió y la mezcla se lavó en suspensión. El residuo se recogió por filtración y se secó para dar el compuesto objeto (6.348 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 9.07 (s, 1H), 7.49–7.44 (m, 2H), 7.39–7.28 (m, 5H), 7.07–7.00 (m, 2H), 5.35 (s, 2H), 4.46 (s, 2H), 4.39 (q, 2H, J = 7.1 Hz), 1.34 (t, 3H, J = 7.1 Hz).

Etapa 2–6

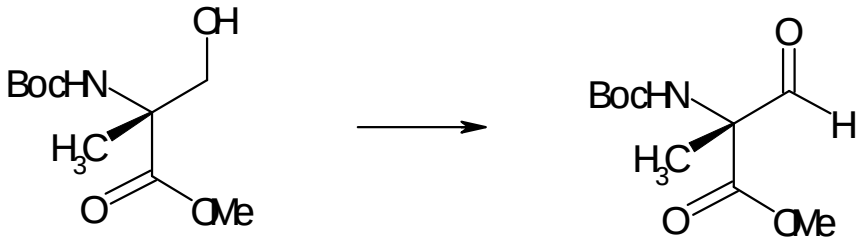


A una solución de ácido (R)–2–ter–butoxicarbonilamino–3–hidroxi–2–metilpropiónico (5.00 g) en dimetilformamida (50 ml) se añadieron carbonato de potasio (6.31 g) y yodometano (2.84 ml) y la mezcla se agitó a temperatura ambiente durante 3 h. El agua (100 ml) se añadió y la mezcla se extrajo con acetato de etilo (150 ml). La capa orgánica se lavó con solución saturada acuosa de hidrógeno–carbonato de

sodio (100 ml), se secó y se concentró para dar el compuesto objeto (5.06 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 5.29 (br s, 1H), 3.99 (dd, 1H, J = 11.6, 6.0 Hz), 3,83–3.73 (m, 1H), 3.78 (s, 3H), 3.23 (br s, 1H), 1.48 (s, 3H), 1.45 (s, 9H).

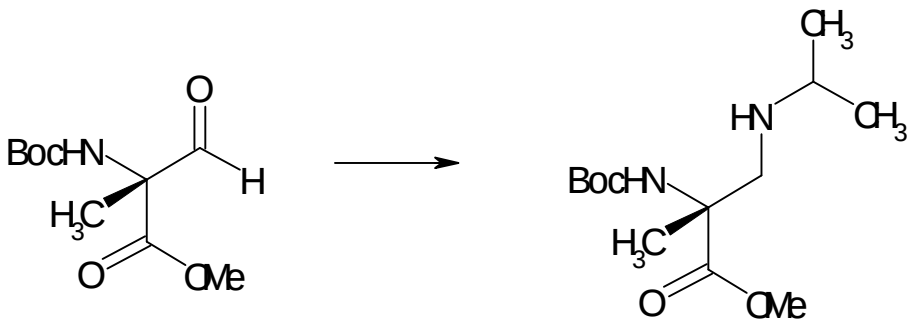
Etapa 2–7



A una solución del compuesto (2.50 g) obtenida en la etapa 2–6 en dimetilsulfóxido (25 ml) se añadieron trietilamina (2.25 ml) y un complejo de piridina–trióxido de azufre (2.62 g) y la mezcla se agitó a temperatura ambiente durante 1 h. Una solución acuosa 1N de ácido clorhídrico (100 ml) se añadió y la mezcla se extrajo con acetato de etilo (200 ml). La capa orgánica se lavó sucesivamente con solución acuosa 1N de ácido clorhídrico (100 ml) y solución saturada acuosa de hidrógeno–carbonato de sodio (100 ml), se secó y se concentró para dar el compuesto objeto (1.22 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 9,57 (s, 1H), 5,63 (br s, 1H), 3,81 (s, 3H), 1,57 (s, 3H), 1,45 (s, 9H).

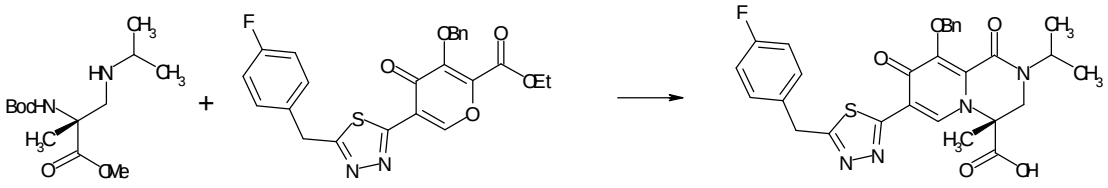
Etapa 2–8



A una solución del compuesto (660 mg) obtenida en la etapa 2–7 en cloroformo (7.0 ml) se añadieron isopropilamina (368 μL), ácido acético (245 μL) y triacetoxiborhidruro de sodio (955 mg) y la mezcla se agitó a temperatura ambiente durante 18 h. Una solución acuosa saturada de hidrógeno–carbonato de sodio (30 ml) y cloroformo (50 ml) se añadieron y la mezcla se dividió. La capa orgánica se lavó con solución saturada acuosa de hidrógeno–carbonato de sodio (30 ml), se secó y se concentró. El concentrado se purificó por cromatografía en columna de gel de sílice (cloroformo:metanol = 10:1) para dar el compuesto objeto (764 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 5.74 (br s, 1H), 3.74 (s, 3H), 2.89 (br s, 2H), 2.73 (sep, 1H, J = 6.2 Hz), 1.52 (s, 3H), 1.44 (s, 9H), 1.02 (d, 3H, J = 6.2 Hz), 1.02 (d, 3H, J = 6.2 Hz).

Etapa 2–9

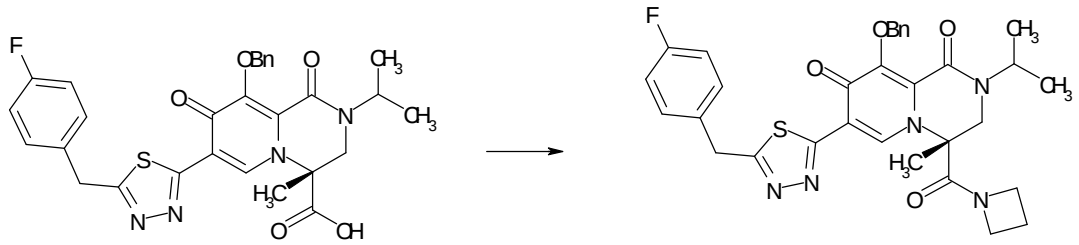


El compuesto (155 mg) obtenido en la etapa 2–8 se disolvió en solución de ácido trifluoroacético (1.0 ml) y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla se concentró, el cloroformo se añadió y la mezcla se concentró. Esta operación se realizó dos veces. Tolueno (5 ml), diisopropiletilamina (395 μL) y el compuesto (200 mg) obtenido en la etapa 2–5 se añadieron y la mezcla se agitó a temperatura ambiente durante 30 min. Tolueno (5 ml) y 1,8–diazabiciclo[5,4,0]undec–7–eno (100 μL) se añadieron y la mezcla se agitó a 120 ºC durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, el ácido acético (1.0 ml) se añadió y la mezcla se agitó luego a 110 ºC durante 1 h. Una solución acuosa 2N de ácido clorhídrico (30 ml) se añadió y la mezcla se extrajo con acetato de etilo (60 ml). La capa orgánica se secó y se concentró, el tolueno se añadió y esta operación se repitió dos veces para dar el compuesto objeto (263 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 8.87 (s, 1H), 7.59 (d, 2H, J = 7.0 Hz), 7.41–7.13 (m, 4H), 7.08–6.98 (m, 3H), 5.46 (d, 1H, J = 10.0 Hz), 5.23 (d, 1H, J = 10.0 Hz), 4.86 (sep, 1H, J = 6.3 Hz), 4.44 (s, 2H), 3.85 (d, 1H, J =

13.5 Hz), 3.44 (d, 1H, J = 13.5 Hz), 1.96 (s, 3H), 1.14 (d, 3H, J = 6.3 Hz), 1.12 (d, 3H, J = 6.3 Hz).

Etapa 2–10

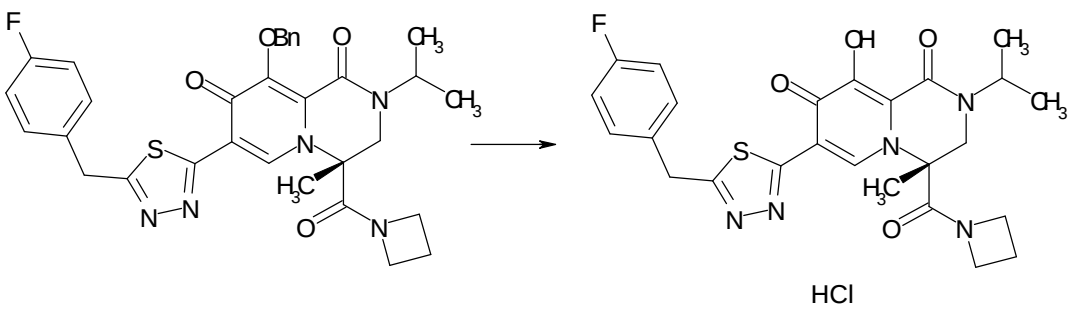


A una solución del compuesto (40.0 mg) obtenido en la etapa 2–9, clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (28.0 mg) e hidrato de 1–hidroxibenzotriazol (22.0 mg) en dimetilformamida (400 μl) se añadió azetidina (20 μl) y la mezcla se agitó a temperatura ambiente durante 18 h. Una solución acuosa saturada de hidrógeno–carbonato de sodio (10 ml) se añadió y la mezcla se extrajo con acetato de etilo (25 ml). La capa orgánica se lavó sucesivamente con solución acuosa 1 N de ácido clorhídrico (10 ml) y solución saturada acuosa de hidrógeno–carbonato de sodio (10 ml), se secó y se concentró. El concentrado se purificó por cromatografía en capa fina de gel de sílice (cloroformo:metanol = 15:1) para dar el compuesto objeto (26.7 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 8.99 (s, 1H), 7.64–7.58 (m, 2H), 7.36–7.27 (m, 5H), 7.07–6.99 (m, 2H), 5.53 (d, 1H, J = 10.0 Hz), 5.39 (d, 1H, J = 10.0 Hz), 4.82 (sep, 1H, J = 6.7 Hz), 4.46 (s, 2H), 4.10–3.92 (m, 2H), 3.97 (d,

1H, J = 13.4 Hz), 3.75–3.66 (m, 1H), 3.61–3.51 (m, 1H), 3.27 (d, 1H, J = 13.4 Hz), 2.19–2.05 (m, 2H), 1.97 (s, 3H), 1.15 (d, 6H, J = 6.7 Hz).

Etapa 2–11

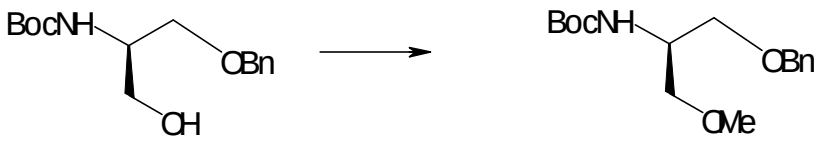


El compuesto (25.0 mg) obtenido en la etapa 2–10 se disolvió en ácido trifluoroacético (1.0 ml) y la mezcla se agitó a temperatura ambiente durante 30 min. La solución de reacción se concentró, se añadió cloroformo y la mezcla se concentró. Se añadió solución 4N de ácido clorhídrico/acetato de etilo y la mezcla se concentró. La cristalización en acetato de etilo–hexano dio el compuesto objeto (17.2 mg) descrito en el esquema antes mencionado.

^{1}H–NMR (DMSO–d_6) δ: 12.91 (br s, 1H), 8.71 (s, 1H), 7.46–7.38 (m, 2H), 7.23–7.15 (m, 2H), 4.70 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.29–4.18 (br m, 1H), 4.02 (d, 1H, J = 13.9 Hz), 3.90–3.81 (br m, 2H), 3.80–3.72 (br m, 1H), 3.71 (d, 1H, J = 13.9 Hz), 2.16–2.04 (br m, 2H), 1.99 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.14 (d, 3H, J = 6.7 Hz).

EJEMPLO 3

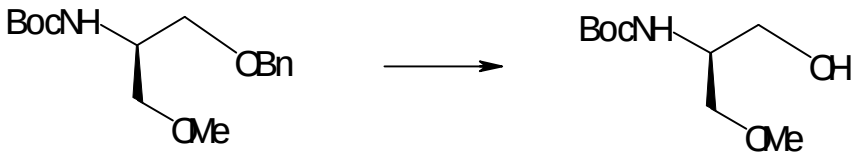
Etapa 3–1



A una solución de éster ter–butílico del ácido (R)–1–benciloximetil–2–hidroxietilcarbámico (5.0 g) y 2,6–di–ter–butilpiridina (8.0 ml) en cloroformo (50 ml) se añadieron yodometano (1.33 ml) y trifluorometansulfonato de plata (I) (6.85 g) bajo enfriamiento con hielo y la mezcla se agitó durante 30 min y luego se agitó a temperatura ambiente durante 1 h. La suspensión de reacción se filtró a través de celite y se concentró y el concentrado se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:20 – 1:4) para dar el compuesto objeto (2.8 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 7.38–7.27 (m, 5H), 4.97–4.85 (m, 1H), 4.53 (s, 2H), 4.00–3.81 (m, 1H), 3.59 (dd, 1H, J = 9.4, 4.2 Hz), 3.51 (dd, 1H, J = 9.4, 5.8 Hz), 3.51 (dd, 1H, J = 9.4, 4.4 Hz), 3.44 (dd, 1H, J = 9.4, 6.0 Hz), 3.34 (s, 3H), 1.44 (s, 9H).

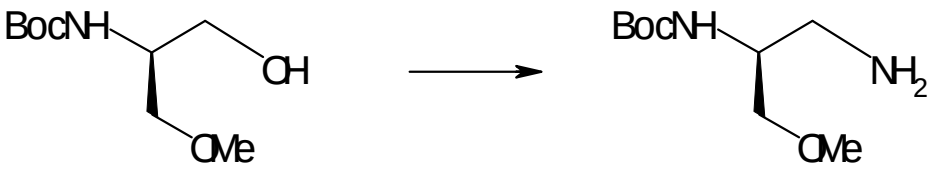
Etapa 3–2



A una solución del compuesto (2.8 g) obtenido en la etapa 3–1 en metanol (100 ml) se añadió un catalizador de paladio–carbón al 7.5% (1.4 g) y la mezcla se agitó a temperatura ambiente durante 17 h bajo una atmósfera de hidrógeno y presión moderada (0.4 MPa). La mezcla de reacción se filtró a través de celite y se concentró para dar el compuesto objeto (2.05 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 5.22–5.10 (m, 1H), 3.84–3.64 (m, 3H), 3.60–3.49 (m, 2H), 3.37 (s, 3H), 2.73–2.55 (m, 1H), 1.45 (s, 9H).

Etapa 3–3

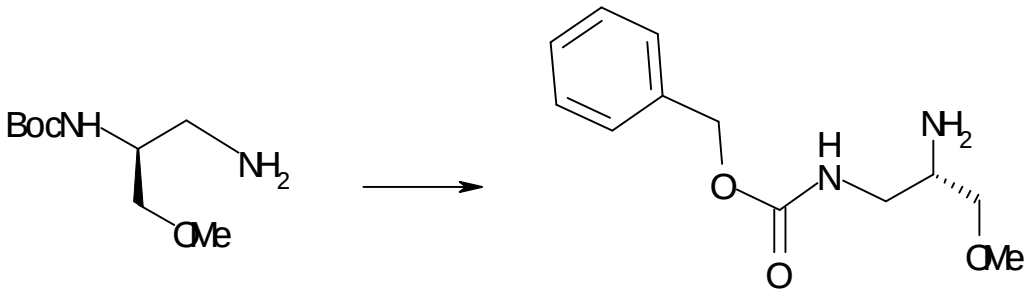


A una solución del compuesto (1.6 g) obtenido en la etapa 3–2, ftalimida (1.38 g) y trifenilfosfina (2.47 g) en tetrahidrofurano (20 ml) se añadieron gota a gota a una solución 2.2M de azodicarboxilato de dietilo/tolueno (4.3 ml) bajo enfriamiento con hielo y la mezcla se agitó a temperatura ambiente durante 20 min. La mezcla de reacción se concentró y el concentrado se purificó por cromatografía en columna de gel de sílice

(acetato de etilo:hexano = 1:10 – 1:2). El sólido obtenido se disolvió en etanol (30 ml)–tolueno (30 ml), monohidrato de hidrazina (1.6 ml) se añadió y la mezcla se agitó a 80 ºC durante 40 min. La mezcla se dejó enfriar hasta temperatura ambiente, el sólido se filtró y el filtrado se concentró. Tolueno se añadió al residuo y el sólido precipitado se filtró. El filtrado se concentró para dar el compuesto objeto (1.3 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 5.08–4.89 (m, 1H), 3.71–3.63 (m, 1H), 3.50 (dd, 1H, J = 9.5, 3.7 Hz), 3.40 (dd, 1H, J = 9.5, 5.1 Hz), 3.35 (s, 3H), 2.84 (dd, 1H, J = 13,0, 6,0 Hz), 2.80 (dd, 1H, J= 13.0, 6.0 Hz), 1.45 (s, 9H).

Etapa 3–4

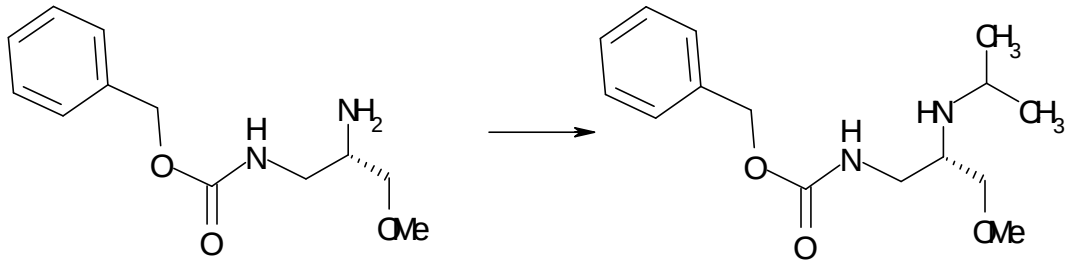


A una solución del compuesto (0.8 g) obtenido en la etapa 3–3 en dioxano (8 ml) se añadió solución saturada acuosa de hidrógeno–carbonato de sodio (2 ml), cloroformiato de bencilo (0.84 ml) se añadió gota a gota bajo enfriamiento con hielo y la mezcla se agitó durante 40 min y a temperatura ambiente durante 10 min. Agua (15 ml) se añadió y la mezcla se extrajo con acetato de etilo. El extracto se secó y se concentró y el

concentrado se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:10 – 1:2). Al sólido obtenido se añadió solución 4N de ácido clorhídrico/dioxano (5 ml) y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se concentró y el residuo se disolvió en cloroformo. Una solución acuosa saturada de hidrógeno–carbonato de sodio (2 ml) se añadió y la mezcla se agitó. La mezcla se extrajo con cloroformo y la capa orgánica se secó y se concentró para dar el compuesto objeto (639 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 7.39–7.28 (m, 5H), 5.27–5.20 (m, 1H), 5.10 (s, 2H), 3.41–3.24 (m, 3H), 3.35 (s, 3H), 3.18–3.01 (m, 2H), 1.39 (br s, 2H).

Etapa 3–5

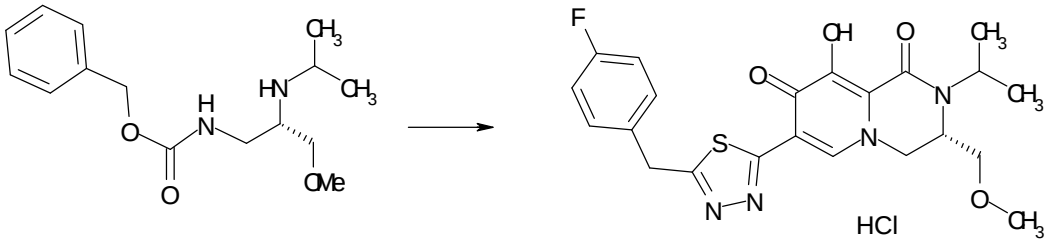


A una solución del compuesto (150 mg) obtenido en la etapa 3–4 en cloroformo (4 ml) se añadieron acetona (70 μl), ácido acético (54 μl) y triacetoxiborhidruro de sodio (200 mg) bajo enfriamiento con hielo y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con cloroformo, se añadió solución saturada acuosa de hidrógeno–carbonato de sodio y la mezcla se agitó. La capa de cloroformo

se lavó con salmuera saturada, se secó y se concentró para dar el compuesto objeto (156 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 7.39–7.28 (m, 5H), 5.39–5.29 (m, 1H), 5.10 (s, 2H), 3.42–3.28 (m, 3H), 3.33 (s, 3H), 3.22–3.14 (m, 1H), 2.96–2.82 (m, 2H), 1.04 (d, 3H, J = 6.8 Hz), 1.02 (d, 3H, J = 6.8 Hz).

Etapa 3–6

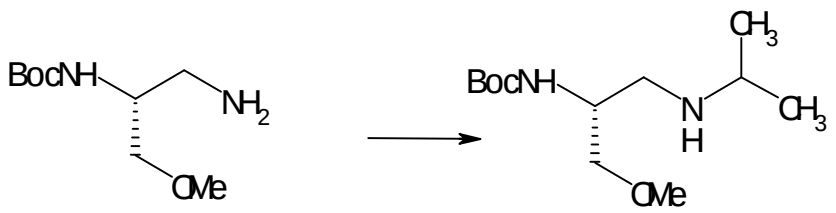


De la misma manera que en la etapa 2–9 y la etapa 2–11, el compuesto objeto (17.0 mg) descrito en el esquema antes mencionado se obtuvo a partir del compuesto (156 mg) obtenido en la etapa 3–5. Para eliminar el grupo protector de amino (grupo benciloxicarbonilo) del compuesto obtenido en la etapa 3–5, se usó un método conocido de acuerdo con el grupo protector.

^{1}H–NMR (DMSO–d_6) δ: 8.84 (s, 1H), 7.43–7.38 (m, 2H), 7.21–7.14 (m, 2H), 4.66 (d, 1H, J = 13.2 Hz), 4.47 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 4.34 (dd, 1H, J = 13.5, 3.7 Hz), 4.22–4.17 (m, 1H), 3.49 (dd, 1H, J = 10.6, 4.3 Hz), 3.39 (dd, 1H, J = 10.6, 7.5 Hz), 3.21 (s, 3H), 1.30 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).

EJEMPLO 4

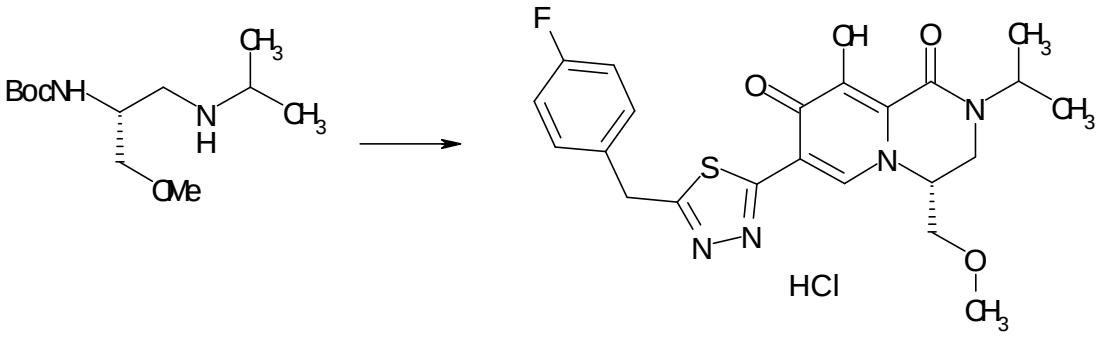
Etapa 4–1



A una solución de éster ter–butílico de ácido (R)–1–aminometil–2–metoxietilcarbámico (1.0 g) producido a partir de éster ter–butílico del ácido (S)–1–benciloximetil–2–hidroxietilcarbámico de la misma manera que en el Ejemplo 3, etapa 3–1 a etapa 3–3 en cloroformo (15 ml) se añadieron acetona (432 μl) y ácido acético (337 μl) bajo enfriamiento con hielo, el triacetoxiborhidruro de sodio (1.25 g) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 14 h. A la mezcla de reacción se añadió solución saturada acuosa de hidrógeno–carbonato de sodio y la mezcla se extrajo 3 veces con cloroformo. La capa de cloroformo combinada se secó y se concentró y el concentrado se purificó por cromatografía en columna de gel de sílice (cloroformo:metanol = 50:1 – 7:1) para dar el compuesto objeto (1.12 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 5.09–4.90 (m, 1H), 3.81–3.69 (m, 1H), 3.49 (dd, 1H, J = 9.5, 4.0 Hz), 3.43–3.37 (m, 1H), 3.34 (s, 3H), 2.82–2.68 (m, 3H), 1.45 (s, 9H), 1.04 (d, 3H, J = 6.4 Hz), 1.03 (d, 3H, J = 6.4 Hz).

Etapa 4–2

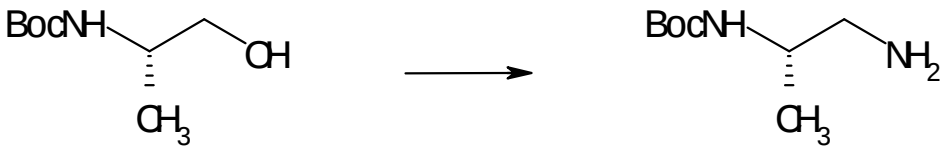


De la misma manera que en la etapa 2–9 y etapa 2–11 (reacciones conocidas de desprotección y condensación se pueden omitir de ser necesario), el compuesto objeto (10.8 mg) descrito en el esquema antes mencionado se obtuvo a partir del compuesto (19.0 mg) obtenido en la etapa 4–1.

^{1}H–NMR (DMSO–d_6) δ: 12.82 (br s, 1H), 8,80 (s, 1H), 7.45–7.38 (m, 2H), 7.23–7.15 (m, 2H), 5.01–4.93 (m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 3.84 (dd, 1H, J = 13.8, 4.1 Hz), 3.75 (dd, 1H, J = 13.8, 1.3 Hz), 3.65–3.54 (m, 2H), 3.25 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).

EJEMPLO 5

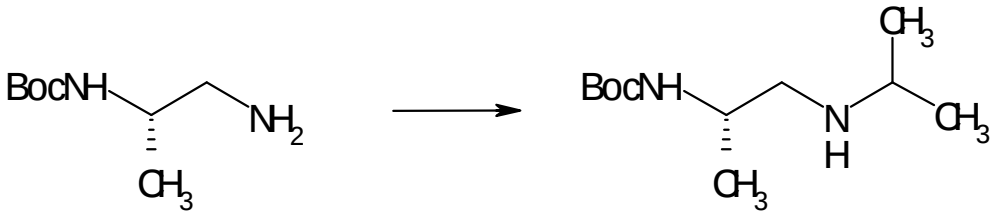
Etapa 5–1



De la misma manera que en la etapa 3–3, el compuesto objeto (1.0 g) descrito en el esquema antes mencionado se obtuvo de éster ter–butílico del ácido (S)–2–hidroxi–1–metiletilcarbámico (1.4 g).

^{1}H–NMR ($CDCl_3$) δ: 4.68–4.49 (m, 1H), 3.71–3.58 (m, 1H), 2.74 (dd, 1H, J = 13.0, 4.9 Hz), 2.62 (dd, 1H, J = 13.0, 6.5 Hz), 1.45 (s, 9H), 1.12 (d, 3H, J= 6.7 Hz).

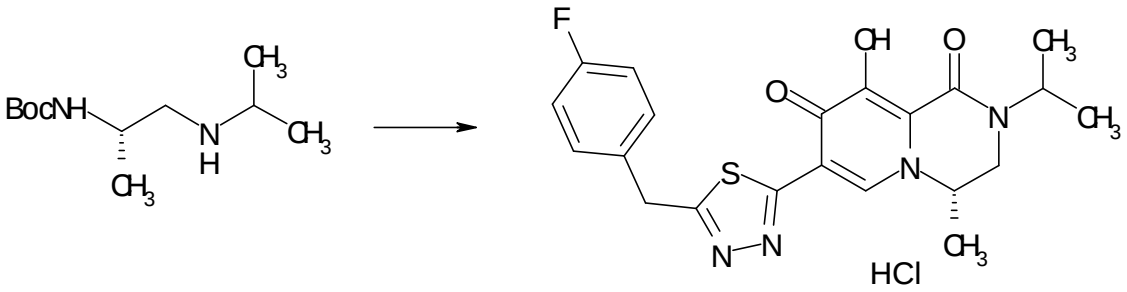
Etapa 5–2



De la misma manera que en la etapa 4–1, el compuesto objeto (180 mg) descrito en el esquema antes mencionado se obtuvo a partir del compuesto (190 mg) obtenido en la etapa 5–1.

^{1}H–NMR ($CDCl_3$) δ: 4.91–4.66 (m, 1H), 3.81–3.66 (m, 1H), 2.81 (sep, 1H, J = 6.4 Hz), 2.66 (dd, 1H, J = 12.0, 4.9 Hz), 2.60 (dd, 1H, J = 12.0, 6.7 Hz), 1.45 (s, 9H), 1.14 (d, 3H, J = 6.6 Hz), 1.06 (d, 6H, J = 6.4 Hz).

Etapa 5–3

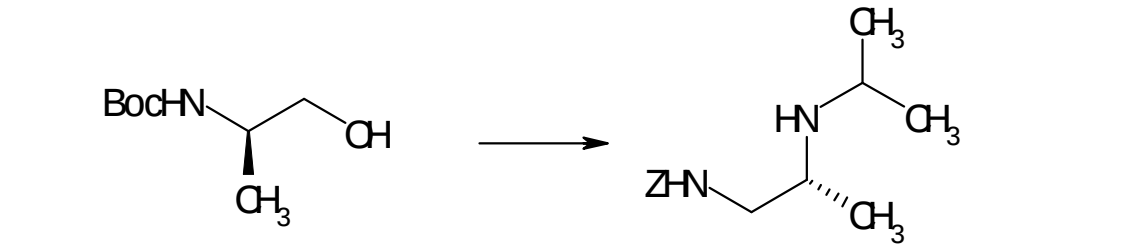


De la misma manera que en la etapa 2–9 y etapa 2–11, el compuesto objeto (27.5 mg) descrito en el esquema antes mencionado se obtuvo a partir del compuesto (30.0 mg) obtenido en la etapa 5–2.

^{1}H–NMR (DMSO–d_6) δ: 12.81 (br s, 1H), 8.91 (s, 1H), 7.45–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.92 (ddd, 1H, J = 6.8, 3.5, 2.2 Hz), 4.80 (t, 1H, J = 6.8 Hz), 4.47 (s, 2H), 3.81 (dd, 1H, J = 13.5, 3.5 Hz), 3.63 (dd, 1H, J = 13.5, 2.2 Hz), 1.39 (d, 3H, J = 6.8 Hz), 1.19 (d, 3H, J = 6.8 Hz), 1.16 (d, 3H, J = 6.8 Hz).

EJEMPLO 6

Etapa 6–1

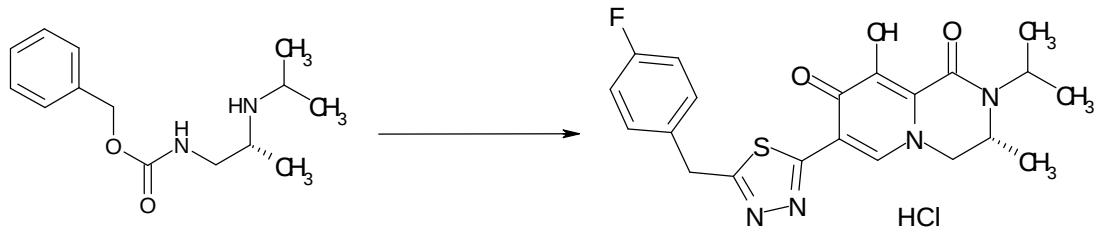


De la misma manera que en la etapa 3–3 a etapa 3–5, el compuesto objeto (105 mg) descrito en el esquema antes mencionado se

obtuvo de éster ter–butílico del ácido (R)–2–hidroxi–1–metiletilcarbámico (2.0 g).

^{1}H–NMR ($CDCl_3$) δ: 7.40–7.28 (m, 5H), 5.28 (br s, 1H), 5.10 (s, 2H), 3.29–3.17 (m, 1H), 3.02–2.92 (m, 1H), 2.92–2.80 (m, 2H), 1.04 (d, 6H, J = 6.3 Hz), 0.99 (d, 3H, J = 6.0 Hz).

Etapa 6–2



De la misma manera que en la etapa 2–9 y etapa 2–11 (reacciones conocidas de desprotección y condensación se pueden omitir de ser necesario), el compuesto objeto (16.6 mg) descrito en el esquema antes mencionado se obtuvo a partir del compuesto (105 mg) obtenido en la etapa 6–1. Para eliminar el grupo protector de amino (grupo benciloxicarbonilo) del compuesto obtenido en la etapa 6–1, se usó un método conocido de acuerdo con el grupo protector.

^{1}H–NMR (DMSO–d_6) δ: 12.54 (br s, 1H), 8.85 (s, 1H), 7.44–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.62–4.53 (m, 1H), 4.51–4.44 (m, 3H), 4.32 (dd, 1H, J = 13.1, 3.4 Hz), 4.26–4.18 (m, 1H), 1.27 (d, 3H, J = 6.7 Hz), 1.26 (d, 3H, J = 6.7 Hz), 1.21 (d, 3H, J = 6.5 Hz).

EJEMPLO 7

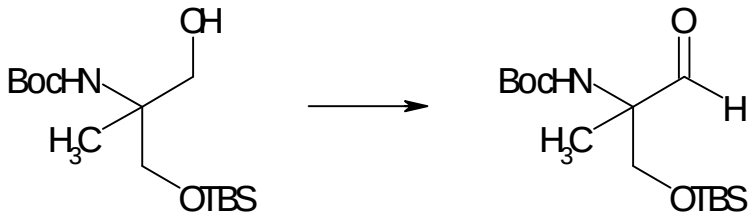
Etapa 7–1



El compuesto 2–amino–2–metil–1,3–propanodiol (20.0 g) se suspendió en tetrahidrofurano (400 ml) y se añadió dicarbonato de di–ter–butilo (41.6 g). La mezcla se agitó a temperatura ambiente durante 3 h y se concentró. Dimetilformamida (200 ml) se añadió para disolver el concentrado nuevamente, se añadieron imidazol (13.0 g) y ter–butilclorodimetilsilano (29.3 g) y la mezcla se agitó a temperatura ambiente durante 15 h. El agua (500 ml) se añadió y la mezcla se extrajo con acetato de etilo (800 ml). La capa orgánica se lavó con agua (400 ml), se secó y se concentró. El concentrado se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:10) para dar el compuesto objeto (35.9 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 5.13 (br s, 1H), 4.00 (br s, 1H), 3.77 (d, 1H, J = 9.7 Hz), 3.70 (dd, 1H, J = 11.4, 4.2 Hz), 3.61 (d, 1H, J = 9.7 Hz), 3.55 (dd, 1H, J = 11.4, 8.4 Hz), 1.44 (s, 9H), 1.19 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

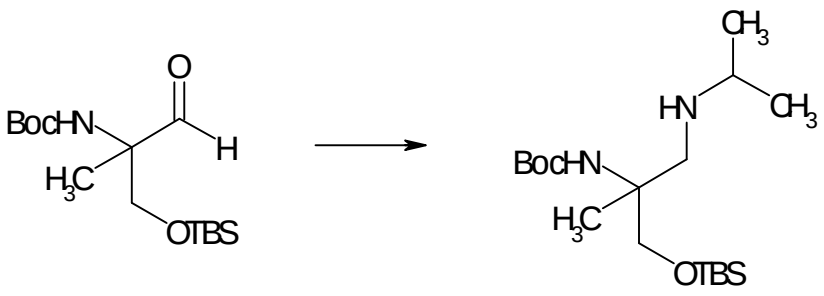
Etapa 7–2



A una solución del compuesto (15.5 g) obtenido en la etapa 7–1 en dimetilsulfóxido (120 ml) se añadieron trietilamina (8.12 ml) y un complejo de trióxido de azufre–piridina (11.9 g) y la mezcla se agitó a temperatura ambiente durante 3 h. Una solución acuosa 1N de ácido clorhídrico (300 ml) se añadió y la mezcla se extrajo con acetato de etilo (700 ml). La capa orgánica se lavó sucesivamente con solución acuosa 1N de ácido clorhídrico (150 ml) y solución saturada acuosa de hidrógeno–carbonato de sodio (200 ml), se secó y se concentró. El concentrado se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:20) para dar el compuesto objeto (11.0 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 9.49 (s, 1H), 5.29 (br s, 1H), 3.86–3.71 (br m, 2H), 1.45 (s, 9H), 1.34 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H).

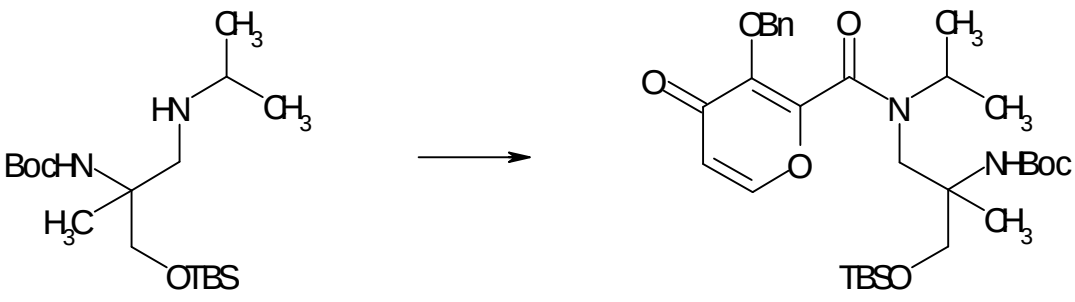
Etapa 7–3



A una solución del compuesto (11.0 g) obtenido en la etapa 7–2 en cloroformo (110 ml) se añadieron isopropilamina (4.46 ml), ácido acético (2.97 ml) y triacetoxiborhidruro de sodio (11.6 g) y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla se dividió en solución saturada acuosa de hidrógeno–carbonato de sodio (150 ml) y cloroformo (200 ml). La capa orgánica se lavó dos veces con solución saturada acuosa de hidrógeno–carbonato de sodio (100 ml), se secó y se concentró. El concentrado se purificó por cromatografía en columna de gel de sílice (cloroformo:metanol = 10:1) para dar el compuesto objeto (14.1 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 5.43 (br s, 1H), 3.73 (d, 1H, J = 9.6 Hz), 3.58 (d, 1H, J = 9.6 Hz), 2.80–2.66 (m, 2H), 2.55 (d, 1H, J = 11.6 Hz), 1.43 (s, 9H), 1.24 (s, 3H), 1.05 (br s, 6H), 0.89 (s, 9H), 0.05 (s, 6H).

Etapa 7–4

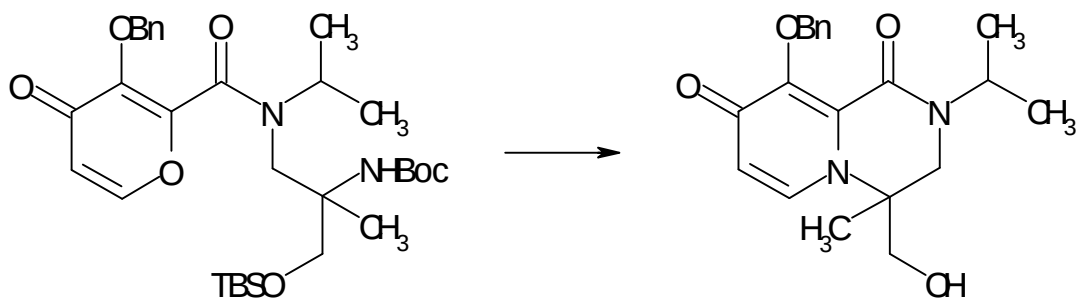


A una solución de ácido 3–benciloxi–4–oxo–4H–piran–2–carboxílico (5.00 g) en tolueno (100 ml) se añadieron trietilamina (3.40 ml) y cloruro de tionilo (1.78 ml) a 0 ºC y la mezcla se agitó a 0 ºC durante 30

min. La sal precipitada se filtró, el filtrado se concentró y el concentrado se disolvió en tetrahidrofurano (40 ml). Esta solución de tetrahidrofurano se añadió gota a gota a una solución del compuesto (10.3 g) obtenida en la etapa 7–3 y piridina (30 ml) en tetrahidrofurano (60 ml) a 0 ºC y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se concentró, se añadió tolueno y la mezcla se concentró. Esta operación se realizó dos veces. Una solución acuosa 1N de ácido clorhídrico (150 ml) se añadió y la mezcla se extrajo con acetato de etilo (250 ml). La capa orgánica se lavó con solución saturada acuosa de hidrógeno–carbonato de sodio (100 ml), se secó y se concentró. El concentrado se purificó por cromatografía en columna de gel de sílice (cloroformo:metanol = 50:1) para dar el compuesto objeto (9.65 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 7.74–7.66 (m, 1H), 7.46–7.28 (m, 5H), 6.50–6.42 (m, 1H), 5.96 (br s, 1H), 5.28–5.14 (m, 2H), 4.02–3.33 (m, 5H), 1.47–1.37 (m, 9H), 1.29–1.00 (m, 9H), 0.95–0.83 (m, 9H), 0.13–0.03 (m, 6H).

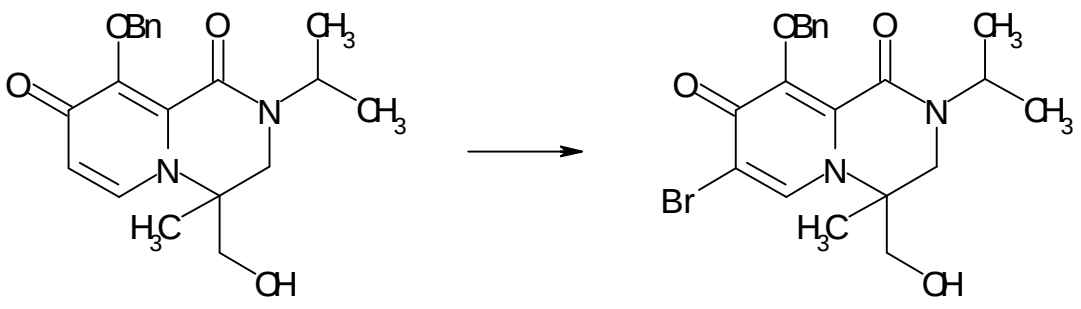
Etapa 7–5



Al compuesto (9.65 g) obtenido en la etapa 7–4 se añadió solución 4N de ácido clorhídrico/acetato de etilo (100 ml) y la mezcla se agitó a temperatura ambiente durante 30 min. Esto se concentró, etanol (400 ml) y solución saturada acuosa de hidrógeno–carbonato de sodio (100 ml) se añadieron y la mezcla se agitó a temperatura ambiente durante 18 h. El material insoluble se filtró y el filtrado se concentró. El agua (100 ml) se añadió y la mezcla se extrajo dos veces con cloroformo (200 ml, 100 ml). La capa orgánica se secó y se concentró y el concentrado se purificó por cromatografía en columna de gel de sílice (cloroformo:metanol = 30:1 – 20:1 – 10:1) para dar el compuesto objeto (2.20 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 7.52 (d, 2H, J = 7.9 Hz), 7.48 (d, 1H, J = 7.9 Hz), 7.37–7.22 (m, 3H), 6.25 (d, 1H, J = 7.9 Hz), 5.79 (br s, 1H), 5.20 (d, 1H, J = 10.0 Hz), 5.17 (d, 1H, J = 10.0 Hz), 4.85 (sep, 1H, J = 6.5 Hz), 3.80 (d, 1H, J = 12.1 Hz), 3.61 (d, 1H, J = 12.1 Hz), 3.35 (d, 1H, J = 14.2 Hz), 3.14 (d, 1H, J = 14.2 Hz), 1.47 (s, 3H), 1.12 (d, 3H, J = 6.5 Hz), 1.11 (d, 3H, J = 6.5 Hz).

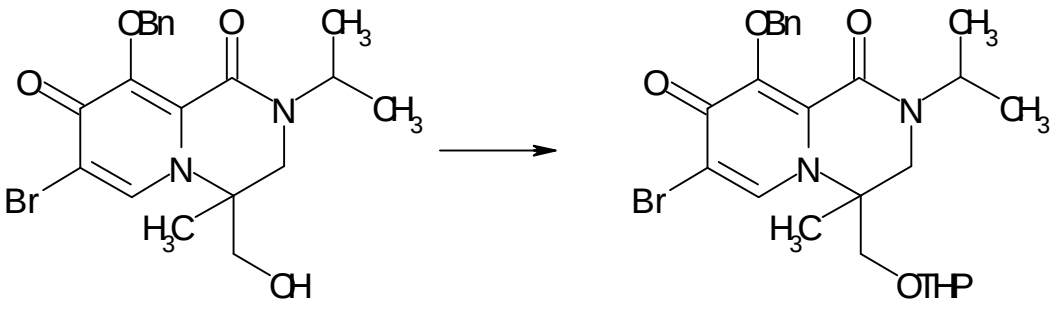
Etapa 7–6



El compuesto (2.20 g) obtenido en la etapa 7–5, tribromuro de trimetilfenilamonio (3.48 g) e hidrógeno–carbonato de sodio (1.04 g) se disolvieron en 2:1 cloroformo–metanol (60 ml) y la mezcla se agitó a temperatura ambiente durante 30 min. Una solución acuosa saturada de hidrógeno–carbonato de sodio (100 ml) se añadió y la mezcla se extrajo con cloroformo (200 ml). La capa orgánica se lavó sucesivamente con solución acuosa 1N de ácido clorhídrico (100 ml) y solución saturada acuosa de hidrógeno–carbonato de sodio (100 ml), se secó y se concentró para dar el compuesto objeto (2.23 g) descrito en el esquema antes mencionado.

^{1}H–NMR (DMSO–d_6) δ: 8.22 (s, 1H), 7.53 (d, 2H, J = 7.0 Hz), 7.41–7.27 (m, 3H), 5.48 (br s, 1H), 5.10 (d, 1H, J = 10.2 Hz), 5.03 (d, 1H, J = 10.2 Hz), 4.67 (sep, 1H, J = 6.7 Hz), 3.66 (d, 1H, J = 11.6 Hz), 3.59 (d, 1H, J = 11.6 Hz), 3.56 (d, 1H, J = 14.2 Hz), 3.45 (d, 1H, J = 14.2 Hz), 1.48 (s, 3H), 1,11 (d, 6H, J = 6.7 Hz).

Etapa 7–7

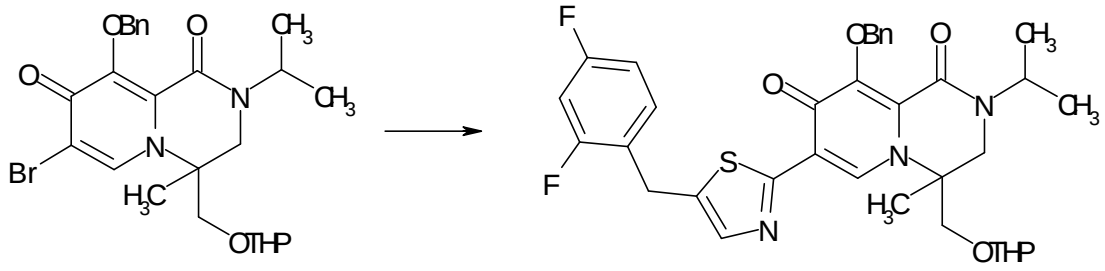


A una solución del compuesto (2.12 g) obtenido en la etapa 7–

6 en cloroformo (45 ml) se añadieron 3,4–dihidro–2H–pirano (882 μl) y ácido canforsulfónico (56 mg) y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró y el concentrado se purificó por cromatografía en columna de gel de sílice (cloroformo:metanol = 30:1) para dar el compuesto objeto (2.23 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 7.91–7.89 (m, 1H), 7.72–7.66 (m, 2H), 7.37–7.27 (m, 3H), 5.41–5.36 (m, 1H), 5.27–5.17 (m, 1H), 5.02–4.92 (m, 1H), 4.61–4.48 (m, 1H), 3.92–3.81 (m, 1H), 3.79–3.27 (m, 5H), 1.78–1.48 (m, 9H), 1.20–1.14 (m, 6H).

Etapa 7–8

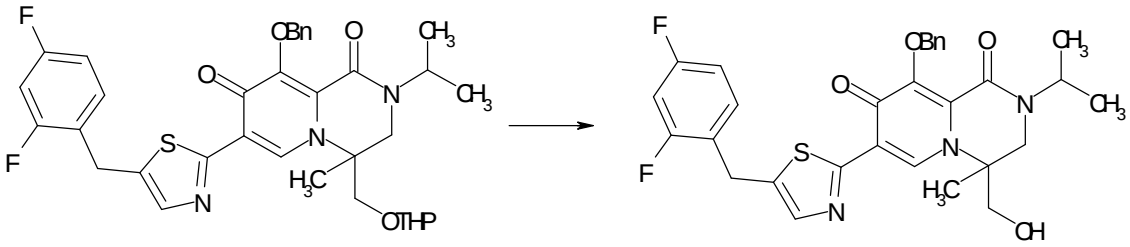


El compuesto (250 mg) obtenido en la etapa 7–7, tris(dibencilidenacetona)dipaladio (44 mg), tri(2–furil)fosfina (45 mg) y 5–(2,4–difluorobencil)–2–tributilstaniltiazol (835 mg) se disolvieron en dioxano (5.0 ml) y la mezcla se calentó en un aparato de microondas a 110 ºC durante 40 min. Esta operación se llevó a cabo dos veces usando las mismas cantidades y las mezclas de reacción se combinaron y se

concentraron. El concentrado se purificó por cromatografía en columna de gel de sílice (cloroformo:metanol = 30:1) para dar el compuesto objeto (682 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 8.78–8.74 (m, 1H), 7.72–7.67 (m, 2H), 7.60–7.56 (m, 1H), 7.37–7.17 (m, 4H), 6.86–6.71 (m, 2H), 5.52–5.46 (m, 1H), 5.34–5.25 (m, 1H), 5.03–4.93 (m, 1H), 4.62–4.53 (m, 1H), 4.20–4.14 (m, 2H), 4.02–3.87 (m, 1H), 3.77–3.43 (m, 5H), 3.36–3.26 (m, 1H), 1.78–1.42 (m, 8H), 1.21–1.13 (m, 6H).

Etapa 7–9

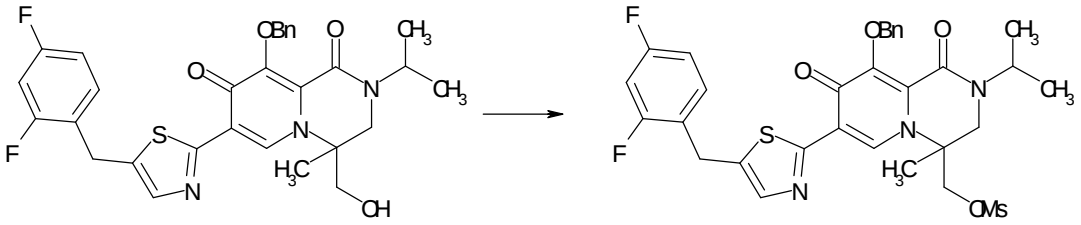


El compuesto (682 mg) obtenido en la etapa 7–8 se disolvió en tetrahidrofurano–metanol–agua (4:1:1, 6.0 ml). El ácido acético (2.0 ml) se añadió y la mezcla se agitó a 80 ºC durante 30 h. La mezcla de reacción se concentró, se añadió tolueno y la mezcla se concentró. Esta operación se llevó a cabo dos veces y el concentrado se purificó por cromatografía en columna de gel de sílice (cloroformo:metanol = 40:1) para dar el compuesto objeto (390 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 8.66 (s, 1H), 7.67–7.62 (m, 2H), 7.51 (s, 1H), 7.36–7.25 (m, 3H), 7.24–7.15 (m, 1H), 6.84–6.75 (m, 2H), 5.40 (d, 1H,

J = 9.7 Hz), 5.29 (d, 1H, J = 9.7 Hz), 4.93 (sep, 1H, J = 6.7 Hz), 4.14 (s, 2H), 3.86 (s, 2H), 3.51 (d, 1H, J = 13.9 Hz), 3.25 (d, 1H, J = 13.9 Hz), 1.65 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.15 (d, 3H, J = 6.7 Hz).

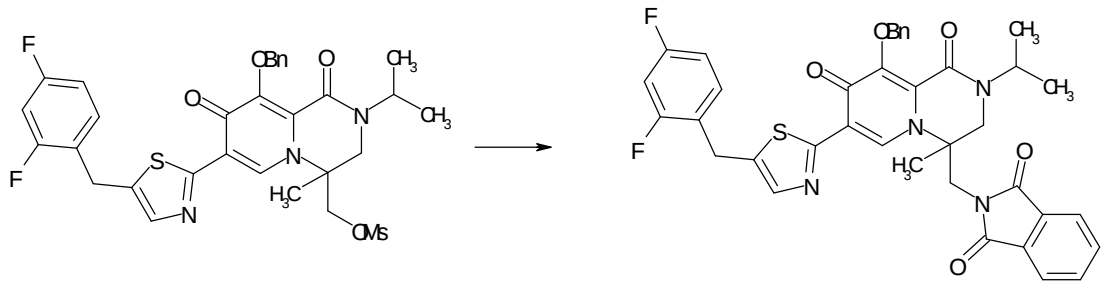
Etapa 7–10



A una solución del compuesto (250 mg) obtenido en la etapa 7–9 en cloroformo (5.0 ml) se añadieron trietilamina (93 μl) y cloruro de metansulfonilo (41 μl) a 0 °C y la mezcla se agitó a 0 ºC durante 1 h. Trietilamina (93 μl) y cloruro de metansulfonilo (41 μl) se añadieron y la mezcla se agitó luego a 0 ºC durante 1 h. Una solución acuosa saturada de hidrógeno–carbonato de sodio (20 ml) se añadió y la mezcla se extrajo con cloroformo (40 ml). La capa orgánica se lavó con solución acuosa 1N de ácido clorhídrico (20 ml), se secó y se concentró para dar el compuesto objeto (295 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 7.68–7.61 (m, 4H), 7.40–7.20 (m, 4H), 6.92–6.82 (m, 2H), 5.45 (d, 1H, J = 9.8 Hz), 5.32 (d, 1H, J = 9.8 Hz), 4.98 (sep, 1H, J = 6.8 Hz), 4.80 (br s, 1H), 4.50 (d, 1H, J = 10.1 Hz), 4.19 (s, 2H), 3.58 (d, 1H, J = 14.1 Hz), 3.37 (d, 1H, J = 14.1 Hz), 3.20 (br s, 3H), 1.85 (s, 3H), 1.22 (d, 3H, J = 6.8 Hz), 1.19 (d, 3H, J = 6.8 Hz).

Etapa 7–11

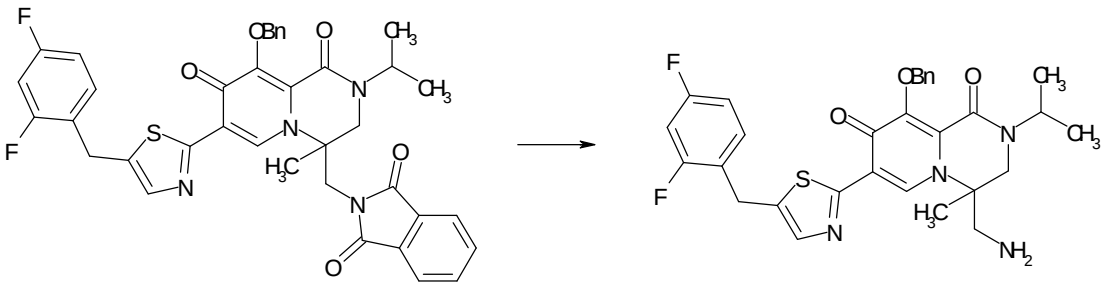


El compuesto (30 mg) obtenido en la etapa 7–10 y ftalimida de potasio (26 mg) se disolvieron en dimetilformamida (1.0 ml) y la mezcla se calentó en un aparato de microondas a 150 ºC durante 2 h. Esta operación se llevó a cabo dos veces más usando el compuesto (115 mg) obtenido en la etapa 7–10, se combinaron la ftalimida de potasio (100 mg) y la dimetilformamida (4.0 ml) y todas las mezclas de reacción. El agua (30 ml) se añadió y la mezcla se extrajo con acetato de etilo (60 ml). La capa orgánica se lavó sucesivamente con solución acuosa 1N de ácido clorhídrico (30 ml) y solución saturada acuosa de hidrógeno–carbonato de sodio (30 ml), se secó y se concentró. El concentrado se purificó por cromatografía en columna de gel de sílice (cloroformo:metanol = 30:1) para dar el compuesto objeto (277 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 8.45 (s, 1H), 7.91–7.58 (m, 7H), 7.40–7.14 (m, 4H), 6.85–6.76 (m, 2H), 5.60 (d, 1H, J = 9.7 Hz), 5.31 (d, 1H, J = 9.7 Hz), 5.07 (sep, 1H, J = 6.7 Hz), 4.21 (d, 1H, J = 14.4 Hz), 4.12 (s, 2H), 3.88 (d, 1H, J = 14.4 Hz), 3.58 (d, 1H, J = 13.9 Hz), 3.47 (d, 1H, J = 13.9 Hz),

1.78 (s, 3H), 1.29 (d, 3H, J = 6.7 Hz), 1.21 (d, 3H, J = 6.7 Hz).

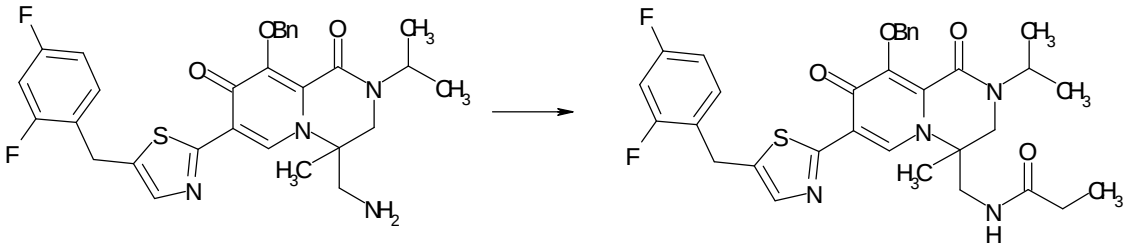
Etapa 7–12



A una solución del compuesto (277 mg) obtenido en la etapa 7–11 en 1:1 etanol–tolueno (6.0 ml) se añadió monohidrato de hidrazina (60 μl) y la mezcla se agitó a 80 ºC durante 3 h. Por otra parte, monohidrato de hidrazina (60 μl) se añadió y la mezcla se agitó a 80 ºC durante 2 h. El precipitado se filtró y el filtrado se concentró y el concentrado se purificó por cromatografía en columna de gel de sílice (cloroformo:metanol = 30:1 – 20:1) para dar el compuesto objeto (104 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 8.71 (s, 1H), 7.71–7.63 (m, 2H), 7.59 (s, 1H), 7.38–7.27 (m, 3H), 7.25–7.16 (m, 1H), 6.85–6.76 (m, 2H), 5.53 (d, 1H, J = 9.7 Hz), 5.26 (d, 1H, J = 9.7 Hz), 4.97 (sep, 1H, J = 6.7 Hz), 4.18 (s, 2H), 3.51 (d, 1H, J = 13.9 Hz), 3.32 (d, 1H, J = 13.9 Hz), 3.05 (d, 1H, J = 13.7 Hz), 2.98 (d, 1H, J = 13.7 Hz), 1.67 (s, 3H), 1.20 (d, 3H, J = 6.7 Hz), 1.18 (d, 3H, J = 6.7 Hz).

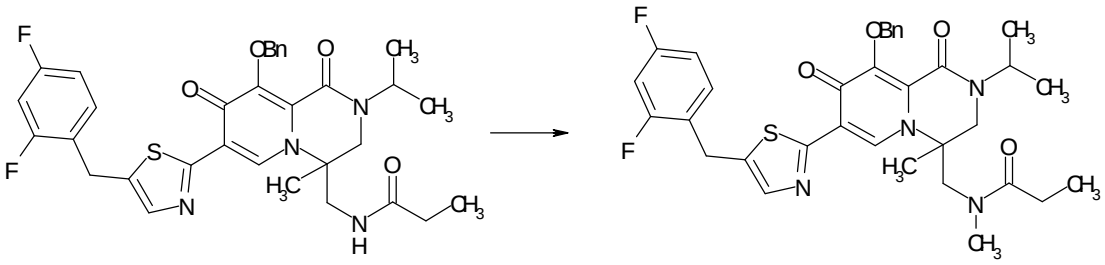
Etapa 7–13



A una solución del compuesto (20.0 mg) obtenido en la etapa 7–12 en cloroformo (400 μl) se añadieron trietilamina (9.9 μl) y cloruro de propionilo (4.8 μl) y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción obtenida se purificó directamente por cromatografía en capa fina de gel de sílice (cloroformo:metanol = 10:1) para dar el compuesto objeto (14.2 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 8.58 (s, 1H), 7.64–7.59 (m, 2H), 7.52 (s, 1H), 7.36–7.27 (m, 3H), 7.25–7.17 (m, 1H), 6.86–6.78 (m, 2H), 6.21 (br s, 1H), 5.40 (d, 1H, J = 9.7 Hz), 5.28 (d, 1H, J = 9.7 Hz), 4.96 (sep, 1H, J = 6.7 Hz), 4.15 (s, 2H), 3.76 (dd, 1H, J = 14.7, 7.1 Hz), 3.55 (dd, 1H, J = 14.7, 6.4 Hz), 3.39 (d, 1H, J = 13.7 Hz), 3.35 (d, 1H, J = 13.7 Hz), 2.28 (dt, 2H, J = 14.5, 6.6 Hz), 1.61 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz), 1.14 (t, 3H, J = 7.7 Hz).

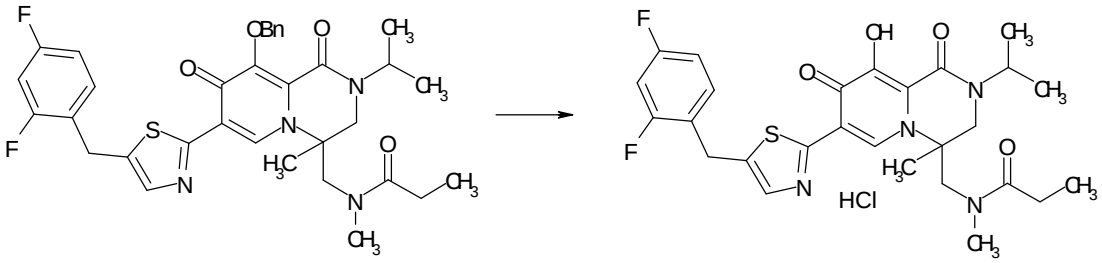
Etapa 7–14



A una solución del compuesto (14.0 mg) obtenido en la etapa 7–13 en tetrahidrofurano (1.0 ml) se añadieron cantidades en exceso de yodometano y ter–butóxido de potasio a 0 °C (hasta la desaparición de los materiales de partida). La mezcla de reacción obtenida se purificó directamente por cromatografía en capa fina de gel de sílice (cloroformo:metanol = 15:1) para dar el compuesto objeto (5.6 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 8.60 (s, 1H), 7.68–7.63 (m, 2H), 7.58 (s, 1H), 7.36–7.27 (m, 3H), 7.25–7.19 (m, 1H), 6.86–6.77 (m, 2H), 5.58 (d, 1H, J = 10.0 Hz), 5.32 (d, 1H, J = 10.0 Hz), 4.98 (sep, 1H, J = 6.7 Hz), 4.28 (d, 1H, J = 14.4 Hz), 4.19 (s, 2H), 3.47 (d, 1H, J = 14.2 Hz), 3.32 (d, 1H, J = 14.2 Hz), 3.12 (d, 1H, J = 14.4 Hz), 2.54 (s, 3H), 2.37 (dq, 1H, J = 15.5, 7.0 Hz), 2.30 (dq, 1H, J = 15.5, 7.0 Hz), 1.69 (s, 3H), 1.21 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz), 1.15 (t, 3H, J = 7.0 Hz).

Etapa 7–15

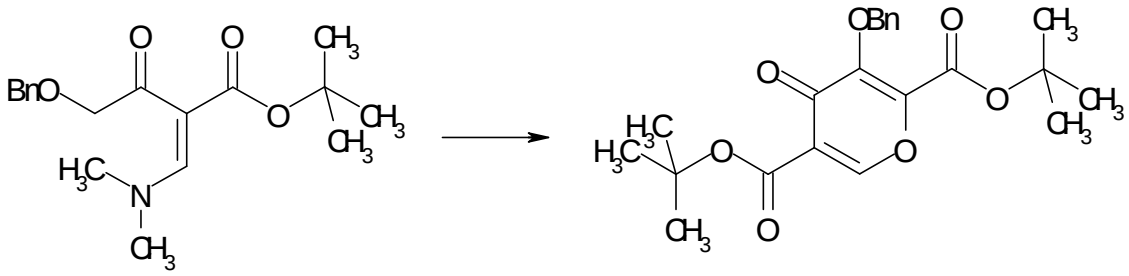


El compuesto (5.6 mg) obtenido en la etapa 7–14 se disolvió en ácido trifluoroacético (1.0 ml) y la mezcla se agitó a temperatura ambiente durante 1 h. La solución de reacción se concentró, se añadió cloroformo y la mezcla se concentró. Se añadió solución 4N de ácido clorhídrico/acetato de etilo y la mezcla se concentró. La cristalización en acetato de etilo–hexano dio el compuesto objeto (3.2 mg) descrito en el esquema antes mencionado.

^{1}H–NMR (DMSO–d_6) δ: 13.18 (br s, 1H), 8.41 (s, 1H), 7.65 (s, 1H), 7.44 (td, 1H, J = 8.8, 6.7 Hz), 7.25 (ddd, 1H, J = 10.2, 9.3, 2.6 Hz), 7.07 (tdd, 1H, J = 8.8, 2.6, 0.9 Hz), 4.80 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 3.83 (d, 1H, J = 14.1 Hz), 3.78 (d, 1H, J = 13.7 Hz), 3.68 (d, 1H, J = 13.7 Hz), 3.51 (d, 1H, J = 14.1 Hz), 2.77 (s, 3H), 2.16–2.03 (m, 2H), 1.67 (s, 3H), 1.22 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz), 0.69 (t, 3H, J = 7.3 Hz).

EJEMPLO 8

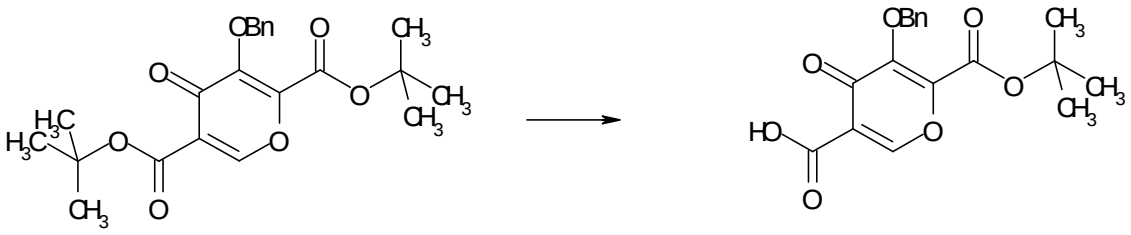
Etapa 8–1



Bajo nitrógeno, una solución 1.6 M de hexametildisilazida de litio–THF (11.73 ml) en THF (100 ml) se enfrió hasta –78 ºC y una solución del compuesto (5 g) obtenido en la etapa 2–2 en THF (15 ml) se añadió gota a gota durante 2 min bajo agitación. Después de agitar durante 13 min, se agregó cloroglioxilato de ter–butilo (3.58 ml) de una vez. Después de agitar durante 25 min, solución saturada acuosa de hidrógeno–sulfato de potasio y acetato de etilo se añadieron y la mezcla se dejó calentar hasta temperatura ambiente. La capa orgánica se separó, se lavó con solución saturada acuosa de hidrógeno–sulfato de potasio y salmuera saturada, se secó sobre sulfato de sodio y se concentró. Se añadió tolueno al residuo y la mezcla se concentró una vez. Tolueno (100 ml) y trietilamina (10 ml) se añadieron y la mezcla se agitó a temperatura ambiente y se concentró 30 min más tarde. La operación antes mencionada se repitió una vez más y ambas se combinaron y se purificaron por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:9 – 1:6) para dar el compuesto objeto (4.496 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 8.37 (s, 1H), 7.52–7.49 (m, 2H), 7.39–7.29 (m, 3H), 5.27 (s, 2H), 1.57 (s, 9H), 1.51 (s, 9H).

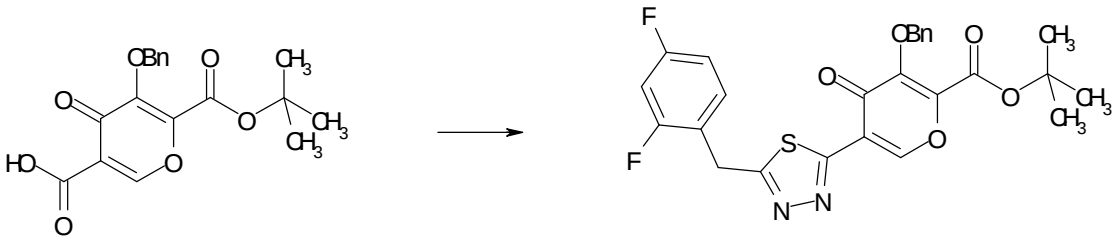
Etapa 8–2



A una solución del compuesto (4.49 g) obtenido en la etapa 8–1 en dioxano (5 ml) se añadió solución 4N de ácido clorhídrico/dioxano (20 ml) con agitación y la mezcla se agitó a temperatura ambiente durante 20 min. La mezcla de reacción se concentró, una solución de acetato de etilo/hexano (1:4) se añadió y la mezcla se lavó en suspensión. El residuo se recogió por filtración y se secó para dar el compuesto objeto (3.30 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 8.78 (s, 1H), 7.48–7.44 (m, 2H), 7.41–7.34 (m, 3H), 5.34 (s, 2H), 1.54 (s, 9H).

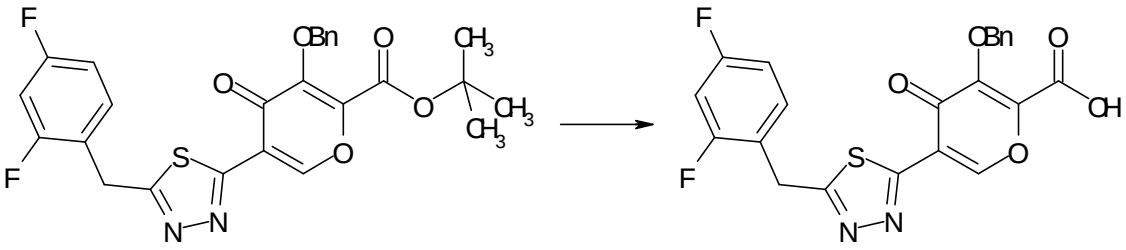
Etapa 8–3



A una solución del compuesto (1 g) obtenido en la etapa 8–2 en tolueno (20 ml)/cloroformo (5 ml) se añadieron cloruro de oxalilo (0.326 ml) y dimetilformamida (0.01 ml) bajo agitación y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se concentró, THF (20 ml) se añadió y la mezcla se enfrió hasta –78 ºC bajo nitrógeno. Trietilamina (1.21 ml) e hidrazida de ácido (2,4–difluorofenil)tioacético (555 mg) se añadieron y la temperatura de la mezcla se elevó lentamente. Después de 25 min, se añadieron acetato de etilo y agua y la mezcla se calentó hasta temperatura ambiente. La mezcla se extrajo dos veces con acetato de etilo y la capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de sodio y se concentró. Al residuo se añadió ácido acético (20 ml) y la mezcla se agitó a 100 ºC durante 2 h. La mezcla se dejó enfriar hasta temperatura ambiente y se concentró. El concentrado se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:9 – 1:4) para dar el compuesto objeto (112 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 9.05 (s, 1H), 7.50–7.46 (m, 1H), 7.39–7.18 (m, 5H), 6.91–6.80 (m, 2H), 5.32 (s, 2H), 4.49 (s, 2H), 1.53 (s, 9H).

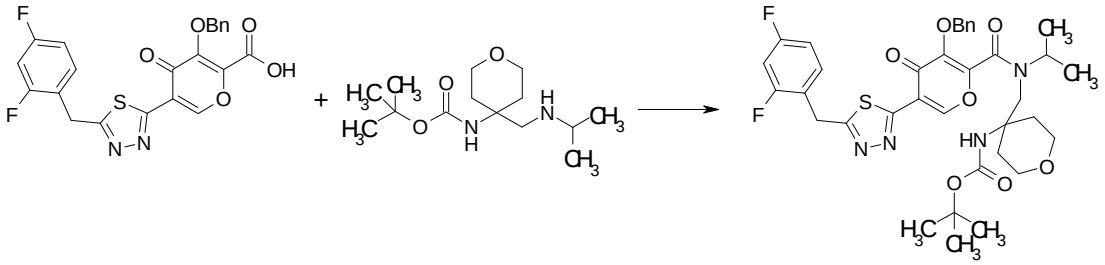
Etapa 8–4



Una solución del compuesto (1.01 g) obtenido en la etapa 8–3 en ácido fórmico (20 ml) se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró, solución de acetato de etilo/hexano (1:4) se añadió y la mezcla se lavó en suspensión. Los cristales se recolectaron por filtración. El licor madre se concentró, se añadió ácido fórmico (20 ml) y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró, una solución de acetato de etilo/hexano (1:4) se añadió y la mezcla se lavó en suspensión. Los cristales se recolectaron por filtración. Ambos cristales se combinaron y se secaron para dar el compuesto objeto (238 mg) descrito en el esquema antes mencionado.

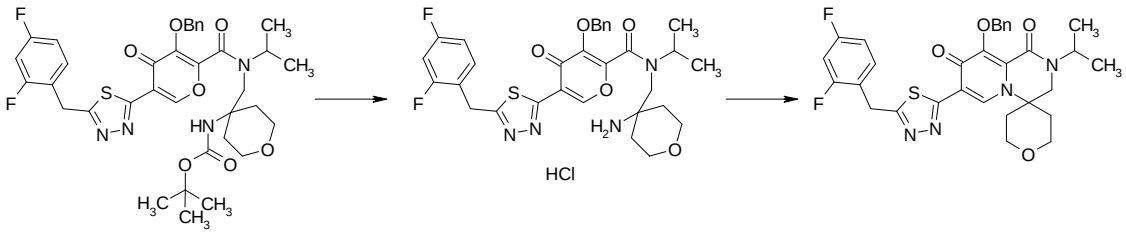
^{1}H–NMR ($CDCl_3$) δ: 9.13 (s, 1H), 7.43–7.18 (m, 6H), 6.93–6.79 (m, 2H), 5.67 (s, 2H), 4.51 (s, 2H).

Etapa 8–5



A una solución del compuesto (69 mg) obtenido en la etapa 8–4 en N,N–dimetilformamida (1.5 ml) se añadieron hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio (HATU) (86 mg), 1–hidroxi–7–azabenzotriazol (HOAt) (31 mg), trietilamina (1.1 ml) y éster ter–butílico del ácido [4–(isopropilaminometil)tetrahidropiran–4–il]carbámico (49 mg) bajo enfriamiento con hielo y la mezcla se agitó a temperatura ambiente durante la noche. A la mezcla de reacción se añadió una solución acuosa al 5% de hidrógeno–sulfato de potasio y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con solución saturada acuosa de hidrógeno–carbonato de sodio, se secó y se concentró. El concentrado se purificó por cromatografía en capa fina de gel de sílice (cloroformo:metanol = 10:1) para dar el compuesto objeto (18 mg) descrito en el esquema antes mencionado.

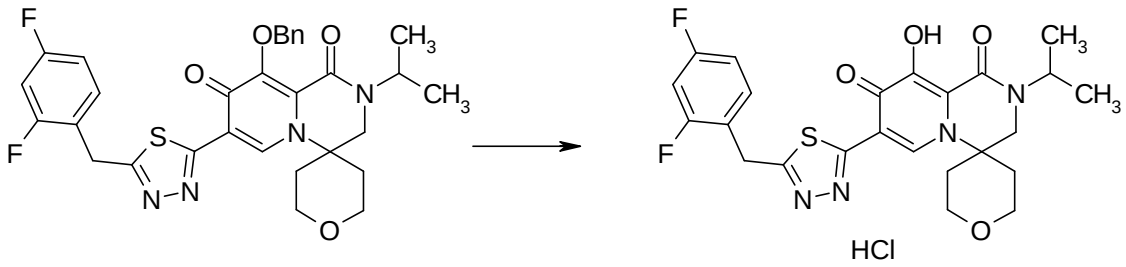
Etapa 8–6



Al compuesto (18 mg) obtenido en la etapa 8–5 se añadió solución 4N de ácido clorhídrico/dioxano (1 ml) y la mezcla se dejó reposar a temperatura ambiente durante 1.5 h. La mezcla de reacción se concentró, 2–propanol (6 ml), agua (0.6 ml) y solución saturada acuosa de hidrógeno–carbonato de sodio (0.6 ml) se añadieron y la mezcla se agitó con calentamiento a 100 ºC durante 4 h. La mezcla se dejó enfriar hasta temperatura ambiente una vez, se dejó reposar durante la noche y se volvió a agitar con calentamiento a 100 ºC durante 8 h. A la mezcla de reacción se añadió salmuera saturada y la mezcla se extrajo con acetato de etilo, se secó y se concentró. El concentrado se purificó por cromatografía en capa fina de gel de sílice (cloroformo:metanol = 10:1) para dar el compuesto objeto (10 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 9.05 (s, 1H), 7.66–7.62 (m, 2H), 7.38–7.28 (m, 4H), 6.88–6.81 (m, 2H), 5.38 (s, 2H), 4.97 (sep, 1H, J = 7.0 Hz), 4.47 (s, 2H), 4.11–4.04 (m, 2H), 3.74–3.65 (m, 2H), 3.55 (s, 2H), 2.45–2.36 (m, 2H), 2.01–1.94 (m, 2H), 1.22 (d, 6H, J = 7.0 Hz).

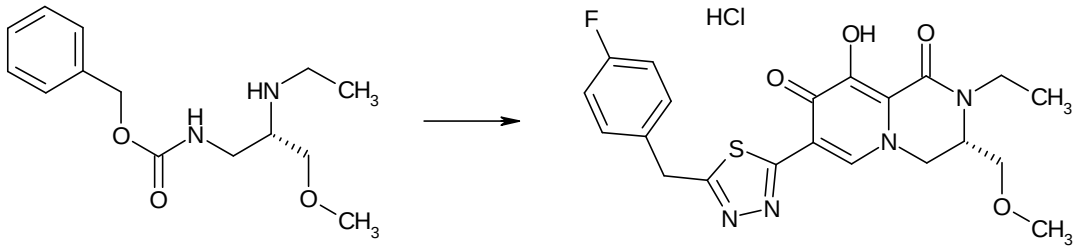
Etapa 8–7



El compuesto (10 mg) obtenido en la etapa 8–6 se disolvió en ácido trifluoroacético (1.0 ml) y la mezcla se dejó reposar a temperatura ambiente durante 50 min. Se concentró una solución de ácido trifluoroacético, se añadió solución 4N de ácido clorhídrico/dioxano y la mezcla se concentró. El tolueno se añadió y la mezcla se concentró. El residuo obtenido se cristalizó en acetato de etilo (0.5 ml)–hexano (2 ml) para dar el compuesto objeto (4.7 mg) descrito en el esquema antes mencionado.

^{1}H–NMR (DMSO–d_6) δ: 13.25 (br s, 1H), 8.88 (s, 1H), 7.58–7.50 (m, 1H), 7.32–7.25 (m, 1H), 7.15–7.09 (m, 1H), 4.83 (sep, 1H, J = 6.9 Hz), 4.50 (s, 2H), 3.89–3.82 (m, 2H), 3.88 (br s, 2H), 3.80–3.73 (m, 2H), 2.31–2.22 (m, 2H), 2.01–1.94 (m, 2H), 1.23 (d, 6H, J = 6.9 Hz).

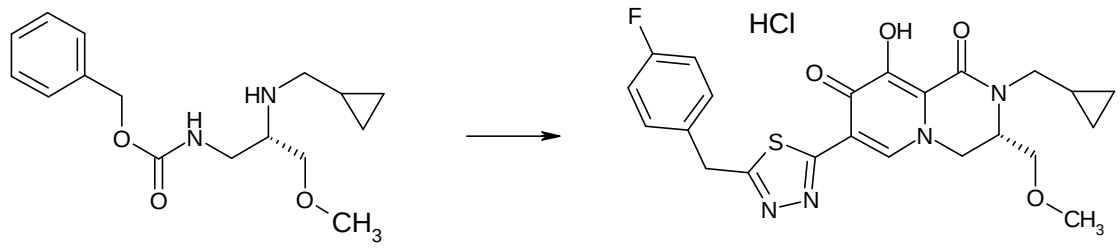
EJEMPLO 9



De la misma manera que en la etapa 2–9 (el grupo protector de amino se eliminó por un método conocido de acuerdo con el grupo protector) y etapa 2–11, el compuesto objeto (18.0 mg) descrito en el esquema antes mencionado se obtuvo de éster bencílico del ácido ((S)–2–etilamino–3–metoxipropil)carbámico (80 mg) que se puede obtener de un compuesto disponible comercialmente por un método conocido.

^{1}H–NMR (DMSO–d_6) δ: 12.64–12.34 (m, 1H), 8.83 (s, 1H), 7.44–7.37 (m, 2H), 7.22–7.14 (m, 2H), 4.64 (dd, 1H, J = 13.4, 1.5 Hz), 4.47 (s, 2H), 4.42 (dd, 1H, J = 13.4, 4.4 Hz), 4.17–4.11 (m, 1H), 3.86 (dq, 1H, J = 14.0, 7.0 Hz), 3.54 (dd, 1H, J = 10.4, 4.9 Hz), 3.50 (dd, 1H, J = 10.4, 6.3 Hz), 3.27 (dq, 1H, J = 14.0, 7.0 Hz), 3.22 (s, 3H), 1.20 (t, 3H, J = 7.0 Hz).

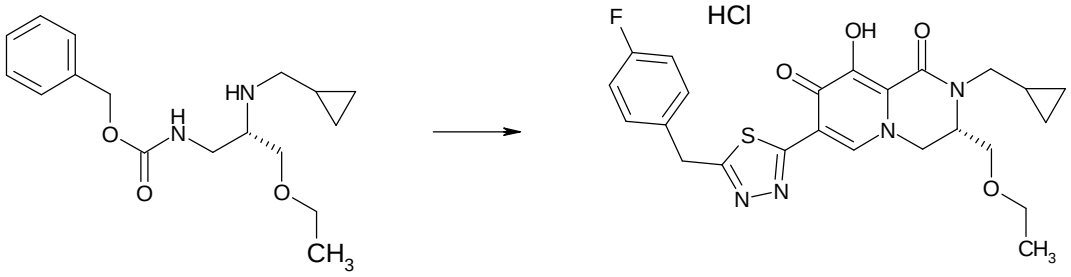
EJEMPLO 10



De la misma manera que en la etapa 2–9 (el grupo protector de amino se eliminó por un método conocido de acuerdo con el grupo protector) y etapa 2–11, el compuesto objeto (10.7 mg) descrito en el esquema antes mencionado se obtuvo de éster bencílico del ácido ((S)–2–ciclopropilmetilamino–3–metoxipropil)carbámico (36 mg) que se puede obtener de un compuesto disponible comercialmente por un método conocido.

^{1}H–NMR (DMSO–d_6) δ: 12.46 (br s, 1H), 8.85 (s, 1H), 7.44–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.67 (dd, 1H, J = 13.7, 1.6 Hz), 4.47 (s, 2H), 4.45 (dd, 1H, J = 13.7, 3.9 Hz), 4.27–4.20 (m, 1H), 3.69 (dd, 1H, J = 14.0, 7.0 Hz), 3.58 (dd, 1H, J = 10.3, 4.8 Hz), 3.51 (dd, 1H, J = 10.3, 6.5 Hz), 3.21 (dd, 1H, J = 14.0, 7.0 Hz), 3.21 (s, 3H), 1.21–1.10 (m, 1H), 0.59–0.47 (m, 2H), 0.44–0.36 (m, 1H), 0.36–0.27 (m, 1H).

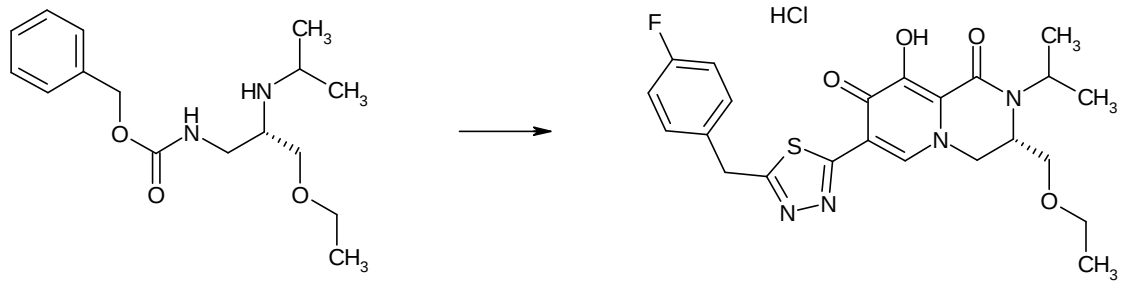
EJEMPLO 11



De la misma manera que en la etapa 2–9 (el grupo protector de amino se eliminó por un método conocido de acuerdo con el grupo protector) y etapa 2–11, el compuesto objeto (32.0 mg) descrito en el esquema antes mencionado se obtuvo de éster bencílico del ácido ((S)–2–ciclopropilmetilamino–3–etoxipropil)carbámico (295 mg) que se puede obtener de un compuesto disponible comercialmente por un método conocido.

^{1}H–NMR (DMSO–d_6) δ: 12.50 (br s, 1H), 8.84 (s, 1H), 7.43–7.38 (m, 2H), 7.21–7.15 (m, 2H), 4.67 (d, 1H, J=12.3 Hz), 4.46 (s, 2H), 4.46–4.42 (m, 1H), 4.22–4.19 (m, 2H), 3.67 (dd, 1H, J=14.2, 7.2 Hz), 3.61 (dd, 1H, J=10.4, 4.4 Hz), 3.55 (dd, 1H, J=10.4, 6.2 Hz), 3.40–3.32 (m, 2H), 3.21 (dd, 1H, J=14.2, 7.0 Hz), 0.94 (t, 3H, J=7,0 Hz), 0.54–0.46 (m, 2H), 0.41–0.37 (m, 1H), 0.33–0.27 (m, 1H).

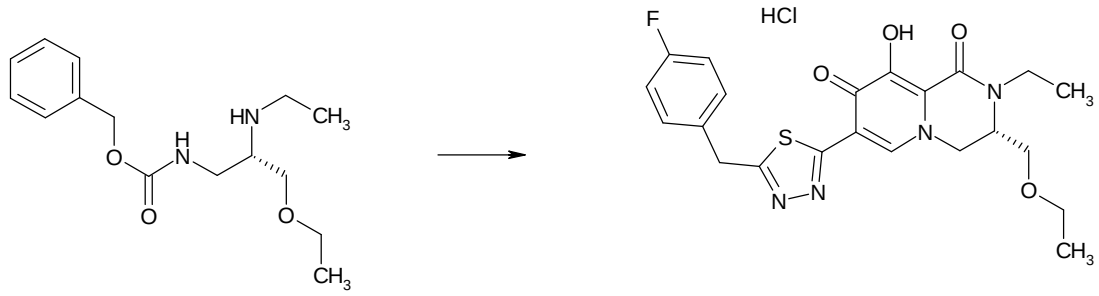
EJEMPLO 12



De la misma manera que en la etapa 2–9 (el grupo protector de amino se eliminó por un método conocido de acuerdo con el grupo protector) y etapa 2–11, el compuesto objeto (35.0 mg) descrito en el esquema antes mencionado se obtuvo de éster bencílico del ácido ((S)–3–etoxi–2–isopropilaminopropil)carbámico (230 mg) que se puede obtener de un compuesto disponible comercialmente por un método conocido.

^{1}H–NMR (DMSO–d_6) δ: 12.40 (br s, 1H), 8.85 (s, 1H), 7.43–7.40 (m, 2H), 7.22–7.16 (m, 2H), 4.67, (d, 1H, J=11.9 Hz), 4.51–4.47 (m, 1H), 4.47 (s, 2H), 4.35 (dd, 1H, J=13.3, 3.9 Hz), 4.20–4.16 (m, 1H), 3.54 (dd, 1H, J=10.5, 4.1 Hz), 3.45–3.32 (m, 3H), 1.30 (d, 3H, J=4.6 Hz), 1.28 (d, 3H, J=4.6 Hz), 0.96 (t, 3H, J=7.0 Hz).

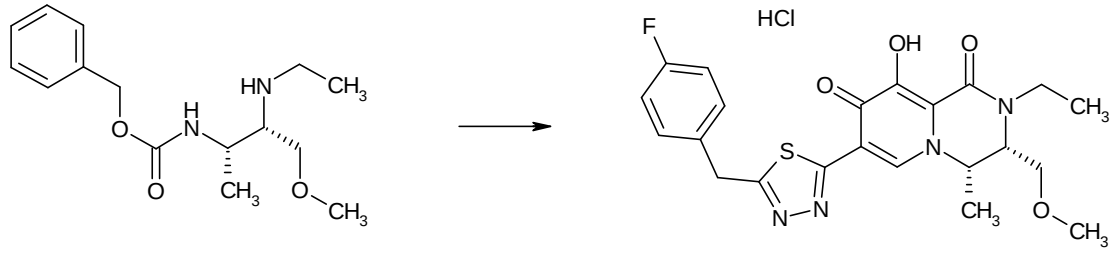
EJEMPLO 13



De la misma manera que en la etapa 2–9 (el grupo protector de amino se eliminó por un método conocido de acuerdo con el grupo protector) y etapa 2–11, el compuesto objeto (37.0 mg) descrito en el esquema antes mencionado se obtuvo de éster bencílico del ácido ((S)–3–etoxi–2–etilaminopropil)carbámico (250 mg) que se puede obtener de un compuesto disponible comercialmente por un método conocido.

^{1}H–NMR (DMSO–d_6) δ: 12.50 (br s, 1H), 8.84 (s, 1H), 7.43–7.40 (m, 2H), 7.22–7.16 (m, 2H), 4.67, (dd, 1H, J=13.5, 1.5 Hz), 4.47 (s, 2H), 4.35 (dd, 1H, J=13.5, 4.2 Hz), 4.14–4.11 (m, 1H), 3.91–3.82 (m, 1H), 3.60–3.53 (m, 2H), 3.41–3.34 (m, 2H), 3.31–3.23 (m, 1H), 1.20 (t, 3H, J=7.2 Hz), 0.96 (t, 3H, J=7.0Hz).

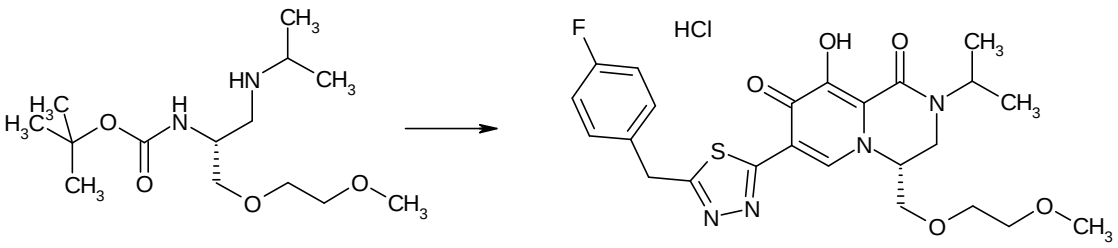
EJEMPLO 14



De la misma manera que en la etapa 2–9 (el grupo protector de amino se eliminó por un método conocido de acuerdo con el grupo protector) y etapa 2–11, el compuesto objeto (32.9 mg) descrito en el esquema antes mencionado se obtuvo de éster bencílico del ácido ((1S,2S)–2–etilamino–3–metoxi–1–metilpropil)carbámico (51 mg) que se puede obtener de un compuesto disponible comercialmente por un método conocido.

^{1}H–NMR (DMSO–d_6) δ: 12.77 (br s, 1H), 8.62 (s, 1H), 7.42–7.38 (m, 2H), 7.20–7.16 (m, 2H), 4.77–4.71 (m, 1H), 4.47 (s, 2H), 4.14 (q, 1H, J=4.0 Hz), 3.92–3.84 (m, 1H), 3.59 (d, 2H, J=4.4 Hz), 3.33–3.26 (m, 1H), 3.18 (s, 3H), 1.64 (d, 3H, J=6.5 Hz), 1.21 (t, 3H, J=7.1 Hz).

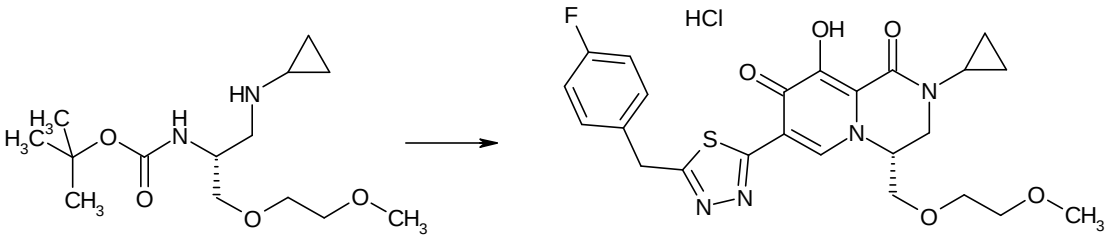
EJEMPLO 15



De la misma manera que en la etapa 2–9 y etapa 2–11, el compuesto objeto (6.2 mg) descrito en el esquema antes mencionado se obtuvo de éster ter–butílico del ácido [(R)–2–isopropilamino–1–((2–metoxietoxi)metil)etil]carbámico ester (19.3 mg) que se puede obtener de un compuesto disponible comercialmente por un método conocido.

^{1}H–NMR (DMSO–d_6) δ: 12.83 (br s, 1H), 8.82 (s, 1H), 7.45–7.38 (m, 2H), 7.23–7.15 (m, 2H), 4.99–4.91 (m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 3.84 (dd, 1H, J = 13.8, 4.1 Hz), 3.78–3.68 (m, 2H), 3.64 (dd, 1H, J = 10.4, 7.7 Hz), 3.58–3.45 (m, 2H), 3.34 (t, 2H, J = 4.5 Hz), 3.11 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).

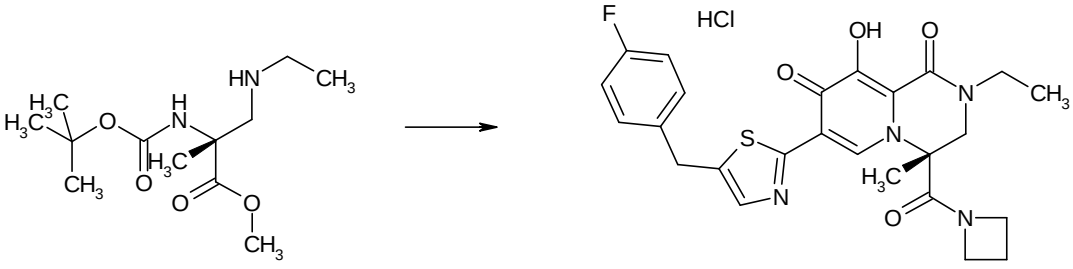
EJEMPLO 16



De la misma manera que en la etapa 2–9 y etapa 2–11, el compuesto objeto (10.7 mg) descrito en el esquema antes mencionado se obtuvo de éster ter–butílico del ácido [(R)–2–ciclopropilamino–1–((2–metoxietoxi)metil)etil]carbámico (16 mg) que se puede obtener de un compuesto disponible comercialmente por un método conocido.

^{1}H–NMR (DMSO–d_6) δ: 8.81 (s, 1H), 7.45–7.37 (m, 2H), 7.22–7.14 (m, 2H), 4.92–4.84 (br m, 1H), 4.47 (s, 2H), 4.09–3.99 (m, 1H), 3.74–3.57 (m, 3H), 3.56–3.44 (m, 2H), 3.34 (t, 2H, J = 4.6 Hz), 3.13 (s, 3H), 2.94–2.84 (m, 1H), 0.97–0.67 (m, 4H).

EJEMPLO 17



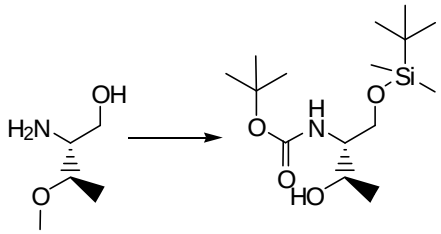
De la misma manera que en la etapa 2–9 a etapa 2–11, el compuesto objeto (39 mg) descrito en el esquema antes mencionado se

obtuvo de éster metílico del ácido (R)–2–ter–butoxicarbonilamino–3–etilamino–2–metilpropiónico (60 mg) que se puede obtener de un compuesto disponible comercialmente por un método conocido.

^{1}H–NMR (DMSO–d_6) δ: 12.69 (m, 1H), 8.60 (s, 1H), 7.69 (s, 1H), 7.34–7.30 (m, 2H), 7.16–7.12 (m, 2H), 4.20 (s, 2H), 4.18–4.13 (m, 1H), 4.01 (d, 1H, J=13.5 Hz), 3.89 (d, 1H, J=13.5 Hz), 3.87–3.80 (m, 2H), 3.67–3.61 (m, 1H), 3.54–3.44 (m, 2H), 2.12–2.04 (m, 2H), 1.91 (s, 3H), 1.10 (t, 3H, J=7.2 Hz).

EJEMPLO 340

Etapa 340–1

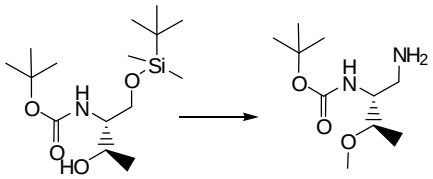


A una solución de L–treoninol (2.05 g) en cloroformo (14 ml) se añadieron dicarbonato de di–ter–butilo (4.26 g) y solución saturada acuosa de hidrógeno–carbonato de sodio (10 ml) y la mezcla se agitó a temperatura ambiente durante 3 h y se dejó reposar durante 3 días. A la mezcla de reacción se añadió salmuera saturada y la mezcla se extrajo con cloroformo. La capa orgánica se secó y se concentró. El residuo obtenido se disolvió en dimetilformamida (40 ml) y, bajo enfriamiento con hielo, imidazol (2.97 g) y ter–butilclorodimetilsilano (1.49 g) se añadieron y la

mezcla se agitó a temperatura ambiente durante 45 min. El agua se añadió y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó y se concentró. El concentrado se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:10 – 1:3) para dar el compuesto objeto (2.39 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 5.18 (d, 1H, J = 8.2 Hz), 4.18–4,14 (m, 1H), 3.89 (dd, 1H, J = 10.4, 3.3 Hz), 3.82 (dd, 1H, J = 10.4, 2.6 Hz), 3.48–3.45 (m, 1H), 3.29 (s, 1H), 1.46 (s, 9H), 1.18 (d, 3H, J = 6.2 Hz), 0.90 (s, 9H), 0.08 (s, 6H).

Etapa 340–2

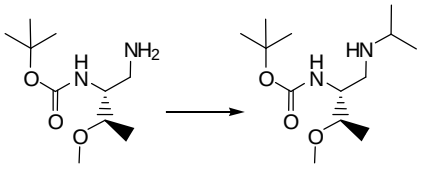


A una solución del compuesto (2.39 g) obtenida en la etapa 340–1 en tolueno (12 ml) se añadieron hidrógeno–sulfato de tetrabutilamonio (76 mg), solución acuosa al 50% de hidróxido de sodio (8 ml) y metilsulfato (922 μl) bajo enfriamiento con hielo y la mezcla se agitó a temperatura ambiente durante 90 min. Se añadió agua helada y la mezcla se extrajo con tolueno. La capa orgánica se lavó con salmuera saturada, se secó y se concentró. El residuo obtenido se disolvió en tetrahidrofurano (20 ml), se añadió solución 1.0 M de fluoruro de

tetrabutilamonio/tetrahidrofurano (8.16 ml) y la mezcla se agitó a temperatura ambiente durante 100 min. El agua se añadió y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó y se concentró. Tolueno se añadió y la mezcla se concentró nuevamente. A una solución del residuo obtenido en tetrahidrofurano (40 ml) se añadieron ftalimida (1.85 g) y trifenilfosfina (3.30 g), solución 2.2 M de azodicarboxilato de dietilo/tolueno (5.05 ml) se añadió gota a gota bajo enfriamiento con hielo y la mezcla se agitó a temperatura ambiente durante 90 min. La mezcla de reacción se concentró y el concentrado se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:10 – 1:2). El sólido obtenido se disolvió en etanol (60 ml)–tolueno (60 ml), monohidrato de hidrazina (2.05 ml) se añadió y la mezcla se agitó a 80 ºC durante 4 h. La mezcla se dejó enfriar hasta temperatura ambiente, el sólido se filtró y el filtrado se concentró. Tolueno se añadió al residuo y el sólido precipitado se filtró. El filtrado se concentró para dar el compuesto objeto (1.54 g) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 4.82 (br s, 1H), 3.52–3.45 (m, 2H), 3.31 (s, 3H), 2.81 (dd, 2H, J = 13.0, 6.0 Hz), 2.76 (dd, 2H, J = 13.0, 7.1 Hz), 1.51 (br s, 2H), 1.15 (d, 3H, J = 6.2 Hz).

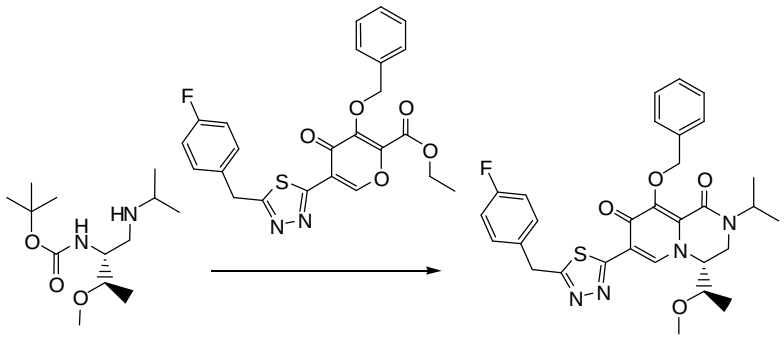
Etapa 340–3



A una solución del compuesto (187 mg) obtenido en la etapa 340–2 en cloroformo (3 ml) se añadieron acetona (76 μl), ácido acético (59 μl) y triacetoxiborhidruro de sodio (218 mg) bajo enfriamiento con hielo y la mezcla se agitó a temperatura ambiente durante 5 h. La mezcla de reacción se diluyó con cloroformo, solución saturada acuosa de hidrógeno–carbonato de sodio se añadió y la mezcla se agitó. La capa de cloroformo se secó y se concentró para dar el compuesto objeto (190 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 4.84 (br s, 1H), 3.59–3.50 (m, 2H), 3.32 (s, 3H), 2.83–2.66 (m, 3H), 1.51 (br s, 1H), 1.14 (d, 3H, J = 6.4 Hz), 1.04 (d, 3H, J = 6.4 Hz), 1.04 (d, 3H, J = 6.4 Hz).

Etapa 340–4

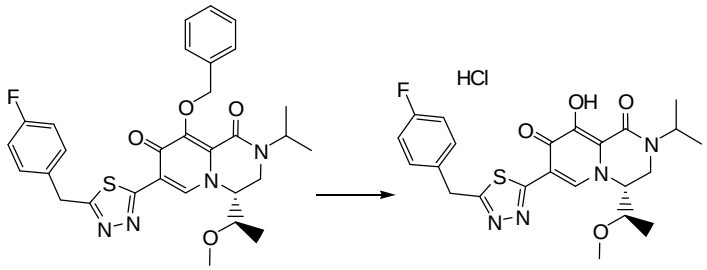


El compuesto (190 mg) obtenido en la etapa 340–3 se disolvió en ácido trifluoroacético (2.0 ml) y la mezcla se dejó reposar a temperatura

ambiente durante 20 min. Se concentró la solución de ácido trifluoroacético, tetrahidrofurano (1.58 ml) y diisopropiletilamina (636 μl) se añadieron para dar una solución. A una solución del compuesto (75 mg) obtenido en la etapa 2–5 en tetrahidrofurano (500 μl) se añadió la solución antes mencionada (634 μl) y la mezcla se agitó a temperatura ambiente durante 15 min. Tolueno (6 ml) y 1,8–diazabiciclo[5,4,0]undec–7–eno (250 μl) se añadieron y la mezcla se agitó a 100 ºC durante 20 min. El ácido acético (750 μl) se añadió y la mezcla se agitó a 100 ºC durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, una solución acuosa al 5% de hidrógeno–sulfato de potasio se añadió y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con solución saturada acuosa de hidrógeno–carbonato de sodio y salmuera saturada, se secó y se concentró. El concentrado se purificó por cromatografía en capa fina de gel de sílice (acetato de etilo:metanol = 15:1) para dar el compuesto objeto (73 mg) descrito en el esquema antes mencionado.

^{1}H–NMR ($CDCl_3$) δ: 8.65 (s, 1H), 7.65–7.62 (m, 2H), 7.35–7.25 (m, 5H), 7.04–6.98 (m, 2H), 5.51 (d, 1H, J = 9.9 Hz), 5.24 (d, 1H, J = 9.9 Hz), 4.94 (sep, 1H, J = 6.8 Hz), 4.43 (s, 2H), 3.93–3.89 (m, 1H), 3.67 (dd, 1H, J = 14.2, 3.9 Hz), 3.47 (dq, 1H, J = 8.8, 6.0 Hz), 3.42 (dd, 1H, J = 14.2, 1.5 Hz), 3.15 (s, 3H), 1.29 (d, 3H, J = 6.0 Hz), 1.19 (d, 3H, J = 6.8 Hz), 1.14 (d, 3H, J = 6.8 Hz).

Etapa 340–5

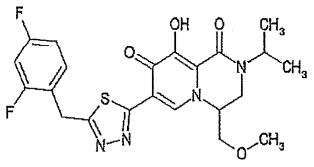
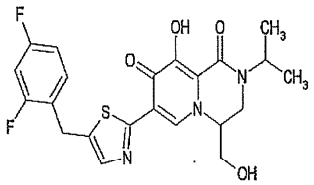
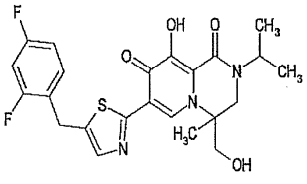


El compuesto (72 mg) obtenido en la etapa 340–4 se disolvió en ácido trifluoroacético (1.0 ml) y la mezcla se dejó reposar a temperatura ambiente durante 4 h. La solución de ácido trifluoroacético se concentró, el tolueno se añadió y la mezcla se concentró. Acetato de etilo, solución 4N de ácido clorhídrico/acetato de etilo y hexano se añadieron para permitir la cristalización para dar el compuesto objeto (65 mg) descrito en el esquema antes mencionado.

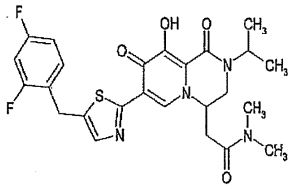
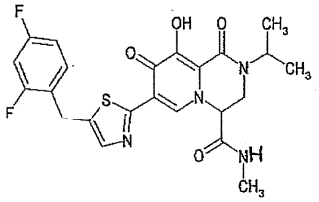
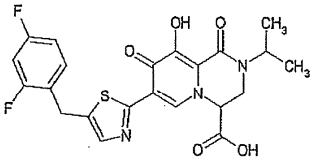
^{1}H–NMR (DMSO–D_6) δ: 12.82 (br s, 1H), 8.72 (s, 1H), 7.44–7.41 (m, 2H), 7.21–7.17 (m, 2H), 4.77 (sep, 1H, J = 6.6 Hz), 4.65 (ddd, 1H, J = 8.2, 4.1, 0.9 Hz), 4.47 (s, 2H), 3.88 (dd, 1H, J = 14.0, 4.1 Hz), 3.76 (dd, 1H, J = 14.0, 0.9 Hz), 3.52 (dq, 1H, J = 8.2, 6.2 Hz), 3.03 (s, 3H), 1.21 (d, 3H, J = 6.2 Hz), 1.20 (d, 3H, J = 6.6 Hz), 1.17 (d, 3H, J = 6.6 Hz).

Los compuestos de los Ejemplos 18 a 465 mostrados en los siguientes cuadros fueron producidos de la misma manera que en los ejemplos 1 a 17 y 340 antes mencionados, o usando otros métodos convencionales de ser necesario. Las fórmulas estructurales y los datos de propiedad de los compuestos de los ejemplos 18 a 465 se muestran en los siguientes cuadros.

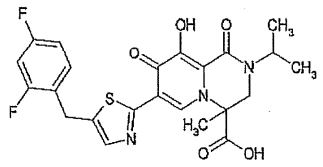
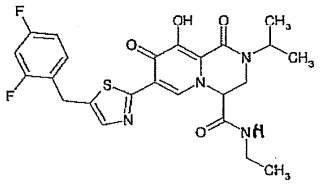
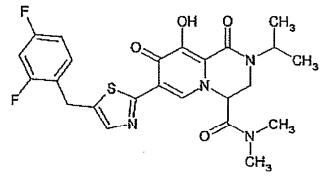
CUADRO 1-1

No.	Fórmula estructural	sal	^{1}H-NMR
18		—	^{1}H-NMR (DMSO-d_6) δ: 12.82 (s, 1H), 8.80 (s, 1H), 7.54 (td, 1H, J = 8.8, 6.7 Hz), 7.29 (ddd, 1H, J = 10.2, 9.3, 2.6 Hz), 7.12 (tdd, 1H, J = 8.8, 2.6 0.9 Hz), 5.01-4.93 (br m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 3.84 (dd, 1H, J = 13.9, 3.9 Hz), 3.75 (dd, 1H, J = 13.9, 1.4 Hz), 3.62 (dd, 1H, J = 10.2, 5.8 Hz), 3.57 (dd, 1H, J = 10.2, 7.7 Hz), 3.25 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
19		—	^{1}H-NMR (DMSO-d_6) δ: 12.69 (br s, 1H), 8.58 (s, 1H), 7.64 (s, 1H), 7.45 (td, 1H, J = 8.8, 6.8 Hz), 7.24 (ddd, 1H, J = 10.6, 9.7, 2.9 Hz), 7.07 (tdd, 1H, J = 8.8, 2.9, 1.0 Hz), 4.75 (sep, 1H, J = 6.6 Hz), 4.69-4.59 (br m, 1H), 4.21 (s, 2H), 3.81 (dd, 1H, J = 13.5, 3.7 Hz), 3.72 (dd, 1H, J = 13.5, 1.5 Hz), 3.67 (dd, 1H, J = 11.7, 5.3 Hz), 3.53 (dd, 1H, J = 11.7, 8.6 Hz), 1.16 (d, 3H, J = 6.6 Hz), 1.15 (d, 3H, J = 6.6 Hz).
20		—	^{1}H-NMR (DMSO-d_6) δ: 13.11 (br s, 1H), 8.60 (s, 1H), 7.66 (s, 1H), 7.44 (td, 1H, J = 8.7, 6.7 Hz), 7.24 (ddd, 1H, J = 10.4, 9.3, 2.8 Hz), 7.07 (tdd, 1H, J = 8.7, 2.8, 0.9 Hz), 4.79 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 3.89 (d, 1H, J = 14.1 Hz), 3.79 (d, 1H, J = 14.1 Hz), 3.72 (d, 1H, J = 13.7 Hz), 3.63 (d, 1H, J = 13.7 Hz), 1.58 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz).

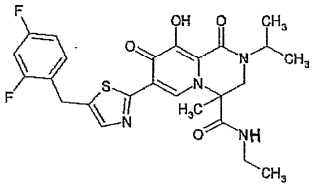
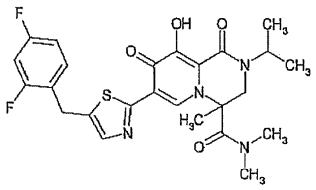
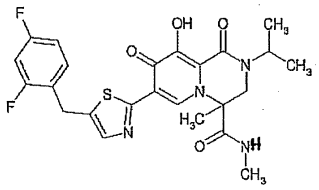
CUADRO 1-2

No.	Fórmula estructural	sal	^{1}H-NMR
21		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.67 (s, 1H), 8.71 (s, 1H), 7.65 (s, 1H), 7.49-7.41 (m, 1H), 7.33-7.20 (m, 1H), 7.11-7.02 (m, 1H), 5.11-5.02 (m, 1H), 4.84-4.73 (m, 1H), 4.21 (s, 2H), 3.87-3.73 (m, 2H), 2.89-2.82 (m, 2H), 2.86 (s, 3H), 2.79 (s, 3H), 1.13 (d, 3H, J = 7.0 Hz), 1.13 (d, 3H, J = 6.7 Hz).
22		—	^{1}H-NMR (DMSO-d_6) δ : 12.37 (s, 1H), 8.66 (s, 1H), 8.25 (q, 1H, J = 4.4 Hz), 7.64 (s, 1H), 7.45 (td, 1H, J = 8.6, 6.5 Hz), 7.25 (ddd, 1H, J = 10.4, 9.5, 2.8 Hz), 7.07 (tdd, 1H, J = 8.6, 2.8, 0.9 Hz), 5.52-5.46 (br m, 1H), 4.69 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.02 (dd, 1H, J = 13.9, 2.1 Hz), 3.94 (dd, 1H, J = 13.9, 3.5 Hz), 2.61 (d, 3H, J = 4.4 Hz), 1.12 (d, 3H, J = 6.7 Hz), 1.03 (d, 3H, J = 6.7 Hz).
23		—	^{1}H-NMR (DMSO-d_6) δ : 12.42 (br s, 1H), 8.75 (s, 1H), 7.65 (s, 1H), 7.46 (td, 1H, J = 8.8, 7.1 Hz), 7.24 (ddd, 1H, J = 10.6, 9.7, 2.4 Hz), 7.07 (tdd, 1H, J = 8.8, 2.4, 0.9 Hz), 5.71-5.66 (br m, 1H), 4.73 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.03 (dd, 1H, J = 13.5, 2.6 Hz), 3.95 (dd, 1H, J = 13.5, 4.0 Hz), 1.16 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz).

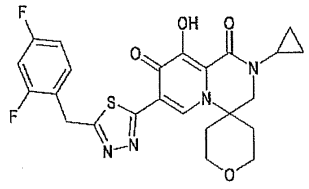
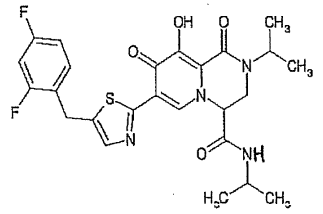
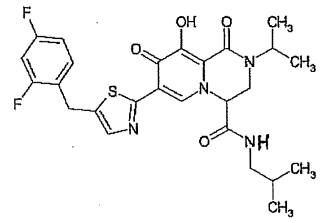
CUADRO 1-3

No.	Fórmula estructural	sal	^{1}H-NMR
24		—	^{1}H-NMR (DMSO-d_6) δ : 12.90 (br s, 1H), 8.59 (s, 1H), 7.66 (s, 1H), 7.44 (td, 1H, J = 9.0, 7.3 Hz), 7.24 (ddd, 1H, J = 10.8, 9.3, 2.4 Hz), 7.07 (tdd, 1H, J = 9.0, 2.4, 1.0 Hz), 4.72 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.05 (d, 2H, J = 13.2 Hz), 3.74 (d, 1H, J = 13.2 Hz), 1.92 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.14 (d, 3H, J = 6.7 Hz).
25		—	^{1}H-NMR (DMSO-d_6) δ : 12.39 (s, 1H), 8.66 (s, 1H), 8.36 (t, 1H, J = 5.4 Hz), 7.64 (s, 1H), 7.45 (td, 1H, J = 8.7, 6.6 Hz), 7.25 (ddd, 1H, J = 10.4, 9.3, 2.6 Hz), 7.07 (tdd, 1H, J = 8.7, 2.6, 0.9 Hz), 5.50-5.43 (br m, 1H), 4.70 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.03 (dd, 1H, J = 13.9, 1.6 Hz), 3.95 (dd, 1H, J = 13.9, 3.7 Hz), 3.09 (qd, 2H, J = 7.4, 5.4 Hz), 1.13 (d, 3H, J = 6.7 Hz), 1.05 (d, 3H, J = 6.7 Hz), 1.02 (t, 3H, J = 7.4 Hz).
26		—	^{1}H-NMR (DMSO-d_6) δ : 12.32 (br s, 1H), 8.71 (s, 1H), 7.63 (s, 1H), 7.46 (td, 1H, J = 8.7, 6.6 Hz), 7.25 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.07 (tdd, 1H, J = 8.7, 2.6, 1.2 Hz), 6.05-6.00 (br m, 1H), 4.71 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 3.98 (dd, 1H, J = 14.4, 3.9 Hz), 3.80 (dd, 1H, J = 14.4, 1.4 Hz), 3.17 (s, 3H), 2.82 (s, 3H), 1.14 (d, 3H, J = 6.7 Hz), 0.98 (d, 3H, J = 6.7 Hz).

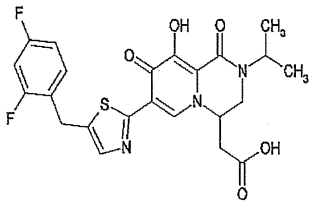
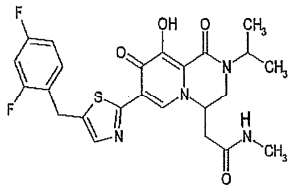
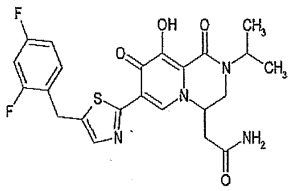
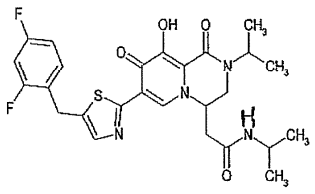
CUADRO 1-4

No.	Fórmula estructural	sal	^{1}H-NMR
27		—	^{1}H-NMR (DMSO-d_6) δ : 12.80 (s, 1H), 8.50 (s, 1H), 8.13 (t, 1H, J = 5.4 Hz), 7.66 (s, 1H), 7.44 (td, 1H, J = 8.7, 6.7 Hz), 7.24 (ddd, 1H, J = 10.4, 9.3, 2.7 Hz), 7.07 (tdd, 1H, J = 8.7, 2.7, 0.9 Hz), 4.71 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.08 (d, 1H, J = 13.8 Hz), 3.78 (d, 1H, J = 13.8 Hz), 3.17-2.98 (m, 2H), 1.92 (s, 3H), 1.15 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz), 1.00 (t, 3H, J = 7.2 Hz).
28		—	^{1}H-NMR (DMSO-d_6) δ : 12.85 (s, 1H), 8.42 (s, 1H), 7.66 (s, 1H), 7.45 (td, 1H, J = 8.7, 6.7 Hz), 7.24 (ddd, 1H, J = 10.4, 9.7, 2.8 Hz), 7.07 (tdd, 1H, J = 8.7, 2.8, 0.9 Hz), 4.73 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.12 (d, 1H, J = 14.1 Hz), 3.79 (d, 1H, J = 14.1 Hz), 2.93 (br s, 6H), 1.97 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz).
29		—	^{1}H-NMR (DMSO-d_6) δ : 12.78 (s, 1H), 8.51 (s, 1H), 8.05 (q, 1H, J = 4.2 Hz), 7.66 (s, 1H), 7.44 (td, 1H, J = 8.7, 6.6 Hz), 7.24 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.07 (tdd, 1H, J = 8.7, 2.6, 0.9 Hz), 4.70 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.05 (d, 1H, J = 13.7 Hz), 3.78 (d, 1H, J = 13.7 Hz), 2.59 (d, 3H, J = 4.2 Hz), 1.92 (s, 3H), 1.14 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.7 Hz).

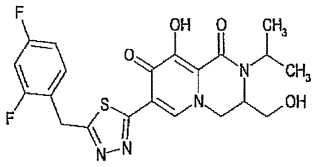
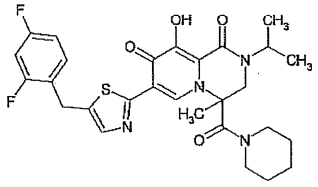
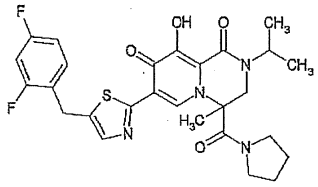
CUADRO 1-5

No.	Fórmula estructural	sal	^{1}H-NMR
30		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.17 (br s, 1H), 8.87 (s, 1H), 7.54 (td, 1H, J = 8.5, 6.9 Hz), 7.29 (ddd, 1H, J = 10.5, 9.3, 2.4 Hz), 7.11 (tdd, 1H, J = 8.5, 2.4, 1.2 Hz), 4.49 (s, 2H), 3.90 (s, 2H), 3.88–3.81 (m, 2H), 3.74–3.66 (m, 2H), 2.98 (ddt, 1H, J = 7.3, 6.9, 4.0 Hz), 2.28–2.19 (m, 2H), 1.98–1.91 (m, 2H), 0.93–0.80 (m, 4H).
31		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.42 (br s, 1H), 8.65 (s, 1H), 8.30 (d, 1H, J = 7.4 Hz), 7.64 (s, 1H), 7.45 (td, 1H, J = 8.6, 6.5 Hz), 7.25 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.07 (tdd, 1H, J = 8.6, 2.6, 0.9 Hz), 5.46–5.41 (br m, 1H), 4.71 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.03 (dd, 1H, J = 14.0, 1.9 Hz), 3.95 (dd, 1H, J = 14.0, 3.6 Hz), 3.85–3.74 (m, 1H), 1.13 (d, 3H, J = 6.7 Hz), 1.09 (d, 3H, J = 6.7 Hz), 1.07 (d, 3H, J = 7.0 Hz), 1.05 (d, 3H, J = 7.0 Hz).
32		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.40 (br s, 1H), 8.68 (s, 1H), 8.31 (dd, 1H, J = 6.2, 5.7 Hz), 7.64 (s, 1H), 7.45 (td, 1H, J = 8.7, 6.6 Hz), 7.24 (ddd, 1H, J = 10.4, 9.3, 2.8 Hz), 7.07 (tdd, 1H, J = 8.7, 2.8, 1.2 Hz), 5.51–5.46 (br m, 1H), 4.68 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.04 (dd, 1H, J = 14.1, 2.1 Hz), 3.94 (dd, 1H, J = 14.1, 3.6 Hz), 2.97 (ddd, 1H, J = 12.8, 6.6, 6.2 Hz), 2.78 (ddd, 1H, J = 12.8, 6.6, 5.7 Hz), 1.67 (sep, 1H, J = 6.5 Hz), 1.12 (d, 3H, J = 6.7 Hz), 1.04 (d, 3H, J = 6.7 Hz), 0.83 (d, 3H, J = 6.5 Hz), 0.82 (d, 3H, J = 6.5 Hz).

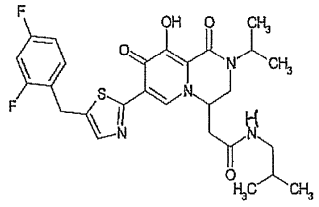
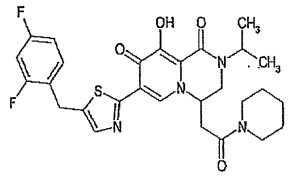
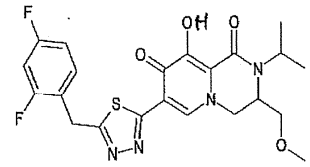
CUADRO 1-6

No.	Fórmula estructural	sal	^{1}H-NMR
33		—	^{1}H-NMR (DMSO-d_6) δ : 8.69 (s, 1H), 7.65 (s, 1H), 7.50-7.40 (m, 1H), 7.33-7.20 (m, 1H), 7.11-7.03 (m, 1H), 5.16-5.04 (m, 1H), 4.84-4.71 (m, 1H), 4.21 (s, 2H), 3.89-3.68 (m, 2H), 2.92-2.64 (m, 2H), 1.15 (t, 6H, J = 6.3 Hz).
34		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.64 (br s, 1H), 8.54 (s, 1H), 7.95-7.87 (m, 1H), 7.64 (s, 1H), 7.50-7.41 (m, 1H), 7.33-7.20 (m, 1H), 7.12-7.03 (m, 1H), 5.08-4.99 (m, 1H), 4.84-4.74 (m, 1H), 4.21 (s, 2H), 3.88-3.65 (m, 2H), 2.70-2.54 (m, 2H), 2.45 (d, 3H, J = 4.4 Hz), 1.17 (d, 3H, J = 6.5 Hz), 1.14 (d, 3H, J = 7.2 Hz).
35		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.58 (s, 1H), 7.65 (s, 1H), 7.49-7.38 (m, 2H), 7.28-7.19 (m, 1H), 7.11-7.03 (m, 1H), 7.00 (br s, 1H), 5.07-4.97 (m, 1H), 4.85-4.73 (m, 1H), 4.21 (s, 2H), 3.91-3.65 (m, 2H), 2.71-2.51 (m, 2H), 1.18 (d, 3H, J = 7.0 Hz), 1.15 (d, 3H, J = 7.2 Hz).
36		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.68 (br s, 1H), 8.46 (s, 1H), 7.85 (d, 1H, J = 7.7 Hz), 7.63 (s, 1H), 7.48-7.39 (m, 1H), 7.29-7.19 (m, 1H), 7.12-7.03 (m, 1H), 5.05-4.94 (m, 1H), 4.86-4.74 (m, 1H), 4.20 (s, 2H), 3.88-3.60 (m, 3H), 2.70-2.46 (m, 2H), 1.18 (d, 3H, J = 7.0 Hz), 1.15 (d, 3H, J = 7.2 Hz), 0.92 (d, 3H, J = 6.7 Hz), 0.69 (d, 3H, J = 6.7 Hz).

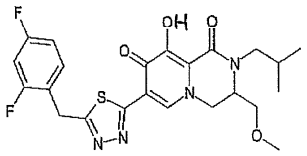
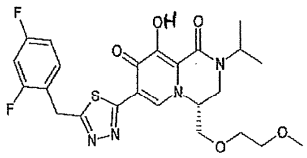
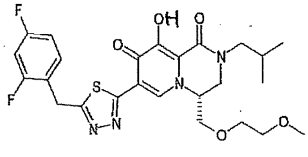
CUADRO 1-7

No.	Fórmula estructural	sal	^{1}H-NMR
37		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.80 (s, 1H), 7.57–7.49 (m, 1H), 7.32–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.67 (dd, 1H, J = 13.2, 1.4 Hz), 4.51 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.34 (dd, 1H, J = 13.2, 3.5 Hz), 4.00–3.93 (m, 1H), 3.57 (dd, 1H, J = 11.5, 3.5 Hz), 3.36 (dd, 1H, J = 11.5, 8.1 Hz), 1.29 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).
38		—	^{1}H-NMR (DMSO-d_6) δ : 12.97 (br s, 1H), 8.38 (s, 1H), 7.67 (s, 1H), 7.45 (td, 1H, J = 8.8, 6.6 Hz), 7.25 (ddd, 1H, J = 10.2, 9.3, 2.6 Hz), 7.07 (tdd, 1H, J = 8.8, 2.6, 0.9 Hz), 4.75 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.03 (d, 1H, J = 13.9 Hz), 3.80 (d, 1H, J = 13.9 Hz), 3.56–3.35 (br m, 4H), 1.90 (s, 3H), 1.59–1.50 (br m, 2H), 1.49–1.40 (br m, 4H), 1.18 (d, 3H, J = 6.7 Hz), 1.14 (d, 3H, J = 6.7 Hz).
39		—	^{1}H-NMR (DMSO-d_6) δ : 12.79 (br s, 1H), 8.52 (s, 1H), 7.66 (s, 1H), 7.45 (td, 1H, J = 8.8, 6.6 Hz), 7.24 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.07 (tdd, 1H, J = 8.8, 2.6, 0.9 Hz), 4.70 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.11 (d, 1H, J = 13.9 Hz), 3.74 (d, 1H, J = 13.9 Hz), 3.64–3.54 (br m, 1H), 3.42–3.32 (br m, 1H), 3.32–3.22 (br m, 1H), 3.15–3.05 (br m, 1H), 2.00 (s, 3H), 1.94–1.82 (br m, 1H), 1.79–1.57 (br m, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.07 (d, 3H, J = 6.7 Hz).

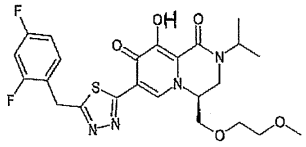
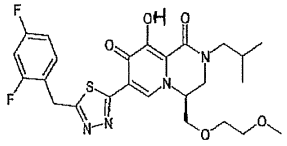
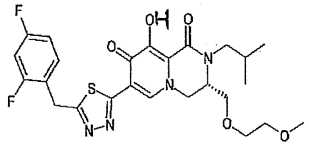
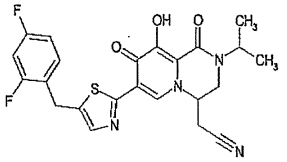
CUADRO 1-8

No.	Fórmula estructural	sal	^{1}H-NMR
40		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.92–12.53 (m, 1H), 8.44 (s, 1H), 7.97 (t, 1H, J = 6.3 Hz), 7.64 (s, 1H), 7.49–7.40 (m, 1H), 7.29–7.19 (m, 1H), 7.12–7.02 (m, 1H), 5.10–4.98 (m, 1H), 4.86–4.75 (m, 1H), 4.21 (s, 2H), 3.90–3.81 (m, 1H), 3.75–3.67 (m, 1H), 2.92–2.82 (m, 1H), 2.77–2.66 (m, 1H), 2.61–2.48 (m, 2H), 1.44–1.30 (m, 1H), 1.18 (d, 3H, J = 7.2 Hz), 1.15 (d, 3H, J = 7.2 Hz), 0.54 (d, 3H, J = 6.7 Hz), 0.50 (d, 3H, J = 7.2 Hz).
41		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.88–12.50 (m, 1H), 8.68 (s, 1H), 7.65 (s, 1H), 7.49–7.40 (m, 1H), 7.28–7.20 (m, 1H), 7.11–7.03 (m, 1H), 5.11–5.03 (m, 1H), 4.84–4.73 (m, 1H), 4.21 (s, 2H), 3.88–3.73 (m, 2H), 3.54–3.19 (m, 4H), 2.87 (d, 2H, J = 7.0 Hz), 1.59–1.43 (m, 2H), 1.42–1.29 (m, 4H), 1.13 (d, 3H, J = 6.7 Hz), 1.13 (d, 3H, J = 6.5 Hz).
42		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.45 (br s, 1H), 8.84 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.07 (m, 1H), 4.66 (dd, 1H, J = 13.4, 1.6 Hz), 4.49 (s, 2H), 4.47 (sep, 1H, J = 6.8 Hz), 4.35 (dd, 1H, J = 13.4, 3.7 Hz), 4.23–4.17 (m, 1H), 3.49 (dd, 1H, J = 10.2, 4.2 Hz), 3.39 (dd, 1H, J = 10.2, 7.4 Hz), 3.21 (s, 3H), 1.30 (d, 3H, J = 6.8 Hz), 1.28 (d, 3H, J = 6.8 Hz).

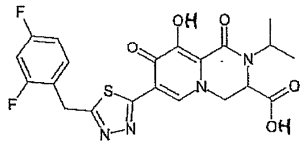
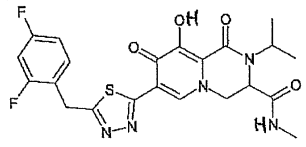
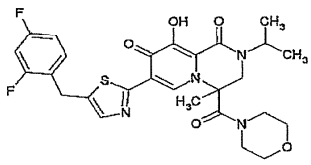
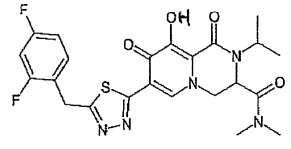
CUADRO 1-9

No.	Fórmula estructural	sal	^{1}H-NMR
43		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.54 (br s, 1H), 8.83 (s, 1H), 7.57–7.49 (m, 1H), 7.32–7.25 (m, 1H), 7.14–7.07 (m, 1H), 4.65 (dd, 1H, J = 13.4, 1.4 Hz), 4.48 (s, 2H), 4.47 (dd, 1H, J = 13.4, 4.3 Hz), 4.10–4.04 (m, 1H), 3.80 (dd, 1H, J = 13.3, 8.0 Hz), 3.53 (dd, 1H, J = 10.4, 5.1 Hz), 3.49 (dd, 1H, J = 10.4, 6.3 Hz), 3.20 (s, 3H), 2.94 (dd, 1H, J = 13.3, 7.1 Hz), 2.08 (ddsep, 1H, J = 8.0, 7.1, 6.7 Hz), 0.95 (d, 3H, J = 6.7 Hz), 0.89 (d, 3H, J = 6.7 Hz).
44		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.84 (br s, 1H), 8.81 (s, 1H), 7.59–7.49 (m, 1H), 7.33–7.23 (m, 1H), 7.16–7.07 (m, 1H), 4.99–4.90 (m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 3.93–3.60 (m, 4H), 3.58–3.44 (m, 2H), 3.33 (t, 2H, J = 4.6 Hz), 3.11 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
45		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.80 (br s, 1H), 8.80 (s, 1H), 7.59–7.50 (m, 1H), 7.35–7.24 (m, 1H), 7.16–7.07 (m, 1H), 4.97–4.86 (m, 1H), 4.49 (s, 2H), 4.06 (dd, 1H, J = 13.7, 4.2 Hz), 3.80–3.66 (m, 3H), 3.59–3.46 (m, 3H), 3.36–3.31 (m, 2H), 3.22 (dd, 1H, J = 7.1, 12.6 Hz), 3.11 (s, 3H), 2.00 (sept, 1H, J = 6.6 Hz), 0.91 (d, 6H, J = 6.6 Hz).

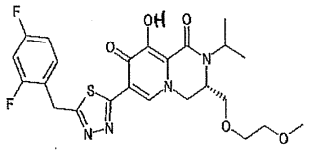
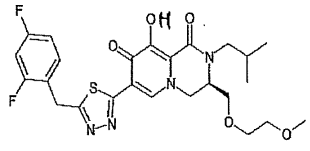
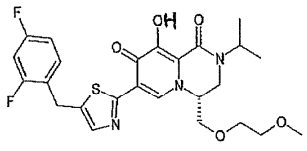
CUADRO 1-10

No.	Fórmula estructural	sal	^{1}H-NMR
46		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.84 (br s, 1H), 8.81 (s, 1H), 7.59–7.49 (m, 1H), 7.33–7.23 (m, 1H), 7.16–7.07 (m, 1H), 4.99–4.90 (m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 3.93–3.60 (m, 4H), 3.58–3.44 (m, 2H), 3.33 (t, 2H, J = 4.6 Hz), 3.11 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
47		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (br s, 1H), 8.80 (s, 1H), 7.59–7.50 (m, 1H), 7.35–7.24 (m, 1H), 7.16–7.07 (m, 1H), 4.97–4.86 (m, 1H), 4.49 (s, 2H), 4.06 (dd, 1H, J = 13.7, 4.2 Hz), 3.80–3.66 (m, 3H), 3.59–3.46 (m, 3H), 3.36–3.31 (m, 2H), 3.22 (dd, 1H, J = 7.1, 12.6 Hz), 3.11 (s, 3H), 2.00 (sept, 1H, J = 6.6 Hz), 0.91 (d, 6H, J = 6.6 Hz).
48		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.55 (br s, 1H), 8.81 (s, 1H), 7.59–7.49 (m, 1H), 7.35–7.24 (m, 1H), 7.16–7.07 (m, 1H), 4.65 (d, 1H, J = 13.2 Hz), 4.53–4.45 (m, 1H), 4.48 (s, 2H), 4.09–4.01 (m, 1H), 3.80 (dd, 1H, J = 13.4, 7.9 Hz), 3.67–3.57 (m, 2H), 3.50–3.39 (m, 2H), 3.30–3.24 (m, 2H), 3.08 (s, 3H), 2.95 (dd, 1H, J = 13.4, 7.0 Hz), 2.14–2.01 (m, 1H), 0.95 (d, 3H, J = 6.5 Hz), 0.90 (d, 3H, J = 6.7 Hz).
49		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.73 (br s, 1H), 8.80 (s, 1H), 7.67 (s, 1H), 7.51–7.42 (m, 1H), 7.29–7.20 (m, 1H), 7.12–7.03 (m, 1H), 5.27–5.17 (m, 1H), 4.85–4.72 (m, 1H), 4.22 (s, 2H), 3.96–3.65 (m, 2H), 3.34–3.20 (m, 2H), 1.20 (d, 3H, J = 7.2 Hz), 1.14 (d, 3H, J = 7.0 Hz).

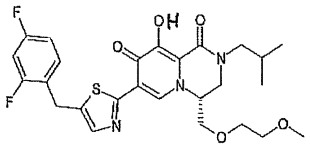
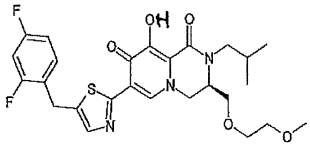
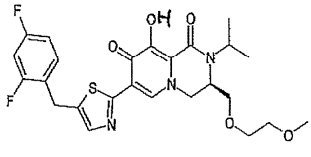
CUADRO 1-11

No.	Fórmula estructural	sal	^{1}H-NMR
50		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.38 (s, 1H), 8.95 (s, 1H), 7.57–7.50 (m, 1H), 7.32–7.25 (m, 1H), 7.14–7.08 (m, 1H), 5.00–4.91 (m, 2H), 4.73 (sep, 1H, J = 6.6 Hz), 4.52 (dd, 1H, J = 13.6, 3.9 Hz), 4.48 (s, 2H), 1.24 (d, 3H, J = 6.6 Hz), 1.13 (d, 3H, J = 6.6 Hz).
51		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.48 (s, 1H), 8.80 (s, 1H), 8.31 (q, 1H, J = 4.6 Hz), 7.57–7.49 (m, 1H), 7.33–7.24 (m, 1H), 7.14–7.07 (m, 1H), 4.76 (d, 1H, J = 14.2 Hz), 4.73 (sep, 1H, J = 6.8 Hz), 4.60 (d, 1H, J = 4.0 Hz), 4.54 (dd, 1H, J = 14.2, 4.0 Hz), 4.48 (s, 2H), 2.60 (d, 3H, J = 4.6 Hz), 1.21 (d, 3H, J = 6.8 Hz), 1.04 (d, 3H, J = 6.8 Hz).
52		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.95 (br s, 1H), 8.39 (s, 1H), 7.68 (s, 1H), 7.45 (td, 1H, J = 8.6, 6.7 Hz), 7.25 (ddd, 1H, J = 10.2, 9.3, 2.6 Hz), 7.07 (tdd, 1H, J = 8.6, 2.6, 0.9 Hz), 4.75 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.02 (d, 1H, J = 14.4 Hz), 3.81 (d, 1H, J = 14.4 Hz), 3.60–3.41 (br m, 8H), 1.91 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
53		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.57 (s, 1H), 8.81 (s, 1H), 7.57–7.49 (m, 1H), 7.32–7.25 (m, 1H), 7.14–7.07 (m, 1H), 5.17 (d, 1H, J = 3.0 Hz), 4.80 (d, 1H, J = 13.7 Hz), 4.70 (sep, 1H, J = 6.7 Hz), 4.52–4.46 (m, 1H), 4.48 (s, 2H), 3.20 (s, 3H), 2.81 (s, 3H), 1.24 (d, 3H, J = 6.7 Hz), 1.00 (d, 3H, J = 6.7 Hz).

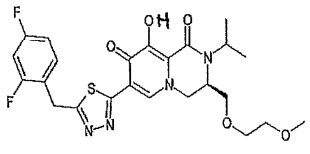
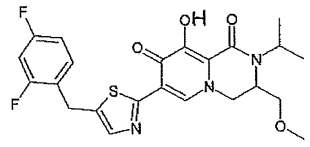
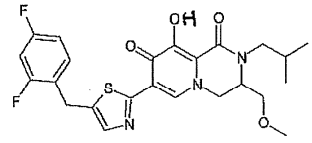
CUADRO 1-12

No.	Fórmula estructural	sal	^{1}H-NMR
54		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.44 (br s, 1H), 8.81 (s, 1H), 7.59-7.48 (m, 1H), 7.34-7.23 (m, 1H), 7.16-7.06 (m, 1H), 4.69-4.61 (m, 1H), 4.53-4.43 (m, 1H), 4.48 (s, 2H), 4.36 (dd, 1H, J = 7.2, 13.4 Hz), 4.23-4.14 (m, 1H), 3.51-3.40 (m, 4H), 3.33-3.25 (m, 2H), 3.08 (s, 3H), 1.28 (d, 3H, J = 6.7 Hz), 1.29 (d, 3H, J = 6.5 Hz).
55		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.55 (br s, 1H), 8.81 (s, 1H), 7.59-7.49 (m, 1H), 7.35-7.24 (m, 1H), 7.16-7.07 (m, 1H), 4.65 (d, 1H, J = 13.2 Hz), 4.53-4.45 (m, 1H), 4.48 (s, 2H), 4.09-4.01 (m, 1H), 3.80 (dd, 1H, J = 13.4, 7.9 Hz), 3.67-3.57 (m, 2H), 3.50-3.39 (m, 2H), 3.30-3.24 (m, 2H), 3.08 (s, 3H), 2.95 (dd, 1H, J = 13.4, 7.0 Hz), 2.14-2.01 (m, 1H), 0.95 (d, 3H, J = 6.5 Hz), 0.90 (d, 3H, J = 6.7 Hz).
56		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.70 (br s, 1H), 8.65 (s, 1H), 7.65 (s, 1H), 7.49-7.42 (m, 1H), 7.28-7.21 (m, 1H), 7.10-7.04 (m, 1H), 4.93-4.87 (m, 1H), 4.77 (sep, 1H, J = 6.9 Hz), 4.21 (s, 2H), 3.82 (dd, 1H, J = 13.7, 4.0 Hz), 3.76-3.67 (m, 2H), 3.62 (dd, 1H, J = 10.5, 7.7 Hz), 3.56-3.45 (m, 2H), 3.35-3.32 (m, 2H), 3.12 (s, 3H), 1.16 (d, 3H, J = 6.9 Hz), 1.15 (d, 3H, J = 6.9 Hz).

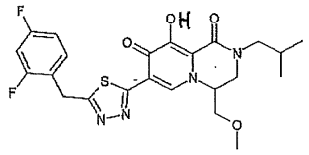
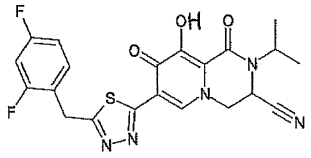
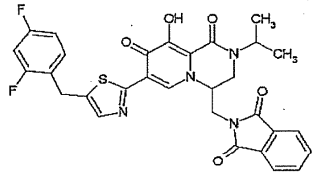
CUADRO 1-13

No.	Fórmula estructural	sal	^{1}H-NMR
57		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.66 (br s, 1H), 8.64 (s, 1H), 7.65 (s, 1H), 7.49–7.42 (m, 1H), 7.28–7.21 (m, 1H), 7.10–7.04 (m, 1H), 4.90–4.82 (m, 1H), 4.21 (s, 2H), 4.04 (dd, 1H, J = 13.7, 4.4 Hz), 3.78–3.64 (m, 3H), 3.56–3.45 (m, 2H), 3.45–3.28 (m, 3H), 3.21 (dd, 1H, J = 13.3, 6.9 Hz), 3.11 (s, 3H), 2.05–1.94 (m, 1H), 0.91 (d, 6H, J = 6.4 Hz).
58		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.40 (br s, 1H), 8.63 (s, 1H), 7.64 (s, 1H), 7.49–7.41 (m, 1H), 7.28–7.20 (m, 1H), 7.11–7.04 (m, 1H), 4.62–4.55 (m, 1H), 4.46 (dd, 1H, J = 13.8, 4.4 Hz), 4.21 (s, 2H), 4.06–4.00 (m, 1H), 3.80 (dd, 1H, J = 13.4, 7.7 Hz), 3.64–3.54 (m, 2H), 3.50–3.40 (m, 2H), 3.33–3.24 (m, 2H), 3.10 (s, 3H), 2.94 (dd, 1H, J = 13.4, 7.1 Hz), 2.12–2.03 (m, 1H), 0.95 (d, 3H, J = 6.7 Hz), 0.89 (d, 3H, J = 6.7 Hz).
59		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.30 (br s, 1H), 8.62 (s, 1H), 7.64 (s, 1H), 7.50–7.40 (m, 1H), 7.29–7.20 (m, 1H), 7.12–7.03 (m, 1H), 4.62–4.55 (m, 1H), 4.48 (sep, 1H, J = 6.7 Hz), 4.36–4.31 (m, 1H), 4.21 (s, 2H), 4.19–4.14 (m, 1H), 3.58 (dd, 1H, J = 10.3, 4.1 Hz), 3.52–3.39 (m, 3H), 3.33–3.27 (m, 2H), 3.10 (s, 3H), 1.29 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).

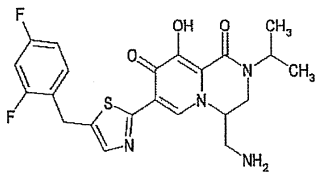
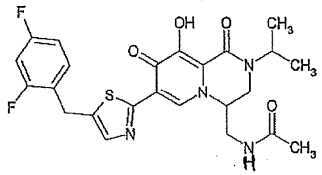
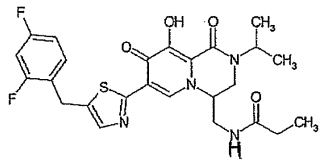
CUADRO 1-14

No.	Fórmula estructural	sal	^{1}H-NMR
60		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.44 (br s, 1H), 8.81 (s, 1H), 7.59–7.48 (m, 1H), 7.34–7.23 (m, 1H), 7.16–7.06 (m, 1H), 4.69–4.61 (m, 1H), 4.53–4.43 (m, 1H), 4.48 (s, 2H), 4.36 (dd, 1H, J = 7.2, 13.4 Hz), 4.23–4.14 (m, 1H), 3.51–3.40 (m, 4H), 3.33–3.25 (m, 2H), 3.08 (s, 3H), 1.28 (d, 3H, J = 6.7 Hz), 1.29 (d, 3H, J = 6.5 Hz).
61		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.66 (s, 1H), 7.49–7.41 (m, 1H), 7.29–7.21 (m, 1H), 7.11–7.03 (m, 1H), 4.60 (dd, 1H, J = 13.4, 1.4 Hz), 4.47 (sep, 1H, J = 6.8Hz), 4.33 (dd, 1H, J = 13.4, 3.7 Hz), 4.22 (s, 2H), 4.14–4.10 (m, 1H), 3.48 (dd, 1H, J = 10.3, 4.3 Hz), 3.36 (dd, 1H, J = 10.3, 7.7 Hz), 3.21 (s, 3H), 1.29 (d, 3H, J = 6.8 Hz), 1.28 (d, 3H, J = 6.8 Hz).
62		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.42 (br s, 1H), 8.65 (s, 1H), 7.65 (s, 1H), 7.50–7.41 (m, 1H), 7.30–7.21 (m, 1H), 7.11–7.03 (m, 1H), 4.59 (dd, 1H, J = 13.7, 1.2 Hz), 4.46 (dd, 1H, J = 13.7, 4.2 Hz), 4.21 (s, 2H), 4.08–4.01 (m, 1H), 3.80 (dd, 1H, J = 13.2, 7.9 Hz), 3.52 (dd, 1H, J = 10.4, 5.4 Hz), 3.48 (dd, 1H, J = 10.4, 6.4 Hz), 3.20 (s, 3H), 2.93 (dd, 1H, J = 13.2, 7.2 Hz), 2.08 (tt, 1H, J = 6.7, 6.7 Hz), 0.95 (d, 3H, J = 6.7 Hz), 0.89 (d, 3H, J = 6.7 Hz).

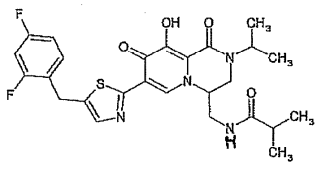
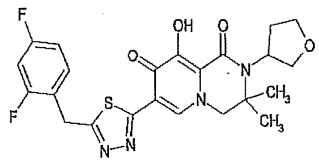
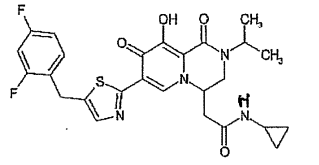
CUADRO 1-15

No.	Fórmula estructural	sal	^{1}H-NMR
63		HCl	^{1}H-NMR ($CDCl_3$) δ : 12.78 (br s, 1H), 9.36 (s, 1H), 7.38–7.30 (m, 1H), 6.92–6.84 (m, 2H), 4.58–4.51 (m, 1H), 4.48 (s, 2H), 4.05–3.98 (m, 1H), 3.76–3.63 (m, 3H), 3.51 (dd, 1H, J = 13.4, 7.9 Hz), 3.39 (s, 3H), 3.29 (dd, 1H, J = 13.4, 7.0 Hz), 2.09–1.99 (m, 1H), 1.00 (d, 3H, J = 6.7 Hz), 0.99 (d, 3H, J = 6.7 Hz).
64		HCl	^{1}H-NMR (DMSO-d_6) δ : 9.03 (s, 1H), 7.59–7.51 (m, 1H), 7.33–7.25 (m, 1H), 7.16–7.08 (m, 1H), 5.66 (dd, 1H, J = 3.0, 1.9 Hz), 5.07 (dd, 1H, J = 13.8, 1.9 Hz), 4.78 (sep, 1H, J = 6.8 Hz), 4.61 (dd, 1H, J = 13.8, 3.0 Hz), 4.51 (s, 2H), 1.31 (d, 3H, J = 6.8 Hz), 1.24 (d, 3H, J = 6.8 Hz).
65		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.31 (s, 1H), 7.78–7.73 (m, 2H), 7.72–7.67 (m, 2H), 7.38 (td, 1H, J = 8.8, 6.8 Hz), 7.36 (s, 1H), 7.25 (ddd, 1H, J = 10.4, 9.0, 2.6 Hz), 7.08 (tdd, 1H, J = 8.8, 2.6, 0.9 Hz), 4.99–4.91 (br m, 1H), 4.80 (sep, 1H, J = 6.7 Hz), 4.13 (s, 2H), 4.04 (dd, 1H, J = 14.3, 4.6 Hz), 3.96 (dd, 1H, J = 13.9, 2.0 Hz), 3.89 (dd, 1H, J = 13.9, 4.0 Hz), 3.82 (dd, 1H, J = 14.3, 9.3 Hz), 1.27 (d, 3H, J = 6.7 Hz), 1.19 (d, 3H, J = 6.7 Hz).

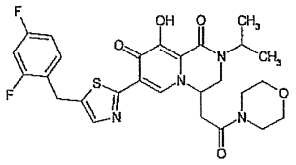
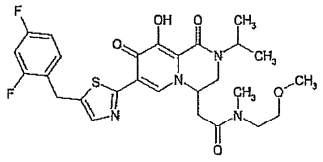
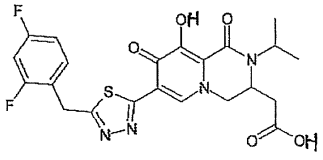
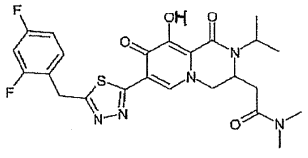
CUADRO 1-16

No.	Fórmula estructural	sal	^{1}H-NMR
66		2HCl	^{1}H-NMR (DMSO-d_6) δ : 12.56 (br s, 1H), 8.70 (s, 1H), 8.25-8.13 (br m, 2H), 7.66 (s, 1H), 7.45 (td, 1H, J = 8.7, 6.7 Hz), 7.25 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.08 (tdd, 1H, J = 8.7, 2.6, 0.9 Hz), 4.95-4.86 (br m, 1H), 4.76 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 3.90 (dd, 1H, J = 13.8, 3.6 Hz), 3.84 (dd, 1H, J = 13.8, 1.9 Hz), 3.35-3.24 (br m, 1H), 3.22-3.09 (br m, 1H), 1.19 (d, 3H, J = 6.7 Hz), 1.15 (d, 3H, J = 6.7 Hz).
67		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.68 (br s, 1H), 8.39 (s, 1H), 8.05 (t, 1H, J = 6.0 Hz), 7.64 (s, 1H), 7.46 (td, 1H, J = 8.8, 7.0 Hz), 7.25 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.08 (tdd, 1H, J = 8.8, 2.6, 0.9 Hz), 4.77 (sep, 1H, J = 6.7 Hz), 4.67-4.59 (br m, 1H), 4.21 (s, 2H), 3.84 (dd, 1H, J = 13.8, 3.8 Hz), 3.74 (dd, 1H, J = 13.8, 0.9 Hz), 3.41-3.27 (m, 2H), 1.66 (s, 3H), 1.19 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
68		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.68 (br s, 1H), 8.36 (s, 1H), 7.97 (t, 1H, J = 6.0 Hz), 7.62 (s, 1H), 7.45 (td, 1H, J = 8.7, 6.7 Hz), 7.25 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.08 (tdd, 1H, J = 8.7, 2.6, 0.9 Hz), 4.77 (sep, 1H, J = 6.7 Hz), 4.68-4.60 (br m, 1H), 4.21 (s, 2H), 3.84 (dd, 1H, J = 13.7, 3.9 Hz), 3.75 (dd, 1H, J = 13.7, 1.4 Hz), 3.40-3.29 (m, 2H), 1.96-1.86 (m, 2H), 1.19 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz), 0.78 (t, 3H, J = 7.5 Hz).

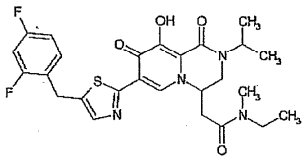
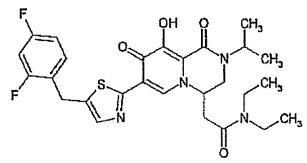
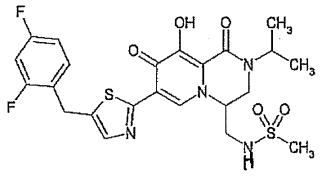
CUADRO 1-17

No.	Fórmula estructural	sal	^{1}H-NMR
69		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.66 (s, 1H), 8.33 (s, 1H), 7.93 (t, 1H, J = 6.0 Hz), 7.61 (s, 1H), 7.43 (td, 1H, J = 8.7, 6.6 Hz), 7.25 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.07 (tdd, 1H, J = 8.7, 2.6, 0.9 Hz), 4.78 (sep, 1H, J = 6.7 Hz), 4.69-4.61 (br m, 1H), 4.20 (s, 2H), 3.84 (dd, 1H, J = 13.7, 3.9 Hz), 3.74 (dd, 1H, J = 13.7, 1.4 Hz), 3.38-3.32 (m, 2H), 2.15 (sep, 1H, J = 6.7 Hz), 1.19 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz), 0.85 (d, 3H, J = 6.7 Hz), 0.73 (d, 3H, J = 6.7 Hz).
70		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.55 (br s, 1H), 8.75 (s, 1H), 7.58-7.50 (m, 1H), 7.34-7.24 (m, 1H), 7.16-7.07 (m, 1H), 4.49 (s, 2H), 4.43-4.30 (m, 3H), 4.03 (q, 1H, J = 7.8 Hz), 3.92-3.48 (m, 3H), 2.36-2.26 (m, 1H), 2.12-2.00 (m, 1H), 1.39 (s, 3H), 1.36 (s, 3H).
71		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.64 (br s, 1H), 8.49 (s, 1H), 8.04 (d, 1H, J = 3.9 Hz), 7.65 (s, 1H), 7.50-7.40 (m, 1H), 7.29-7.20 (m, 1H), 7.11-7.03 (m, 1H), 5.07-4.96 (m, 1H), 4.84-4.72 (m, 1H), 4.21 (s, 2H), 3.87-3.59 (m, 2H), 2.71-2.30 (m, 3H), 1.15 (t, 6H, J = 7.4 Hz), 0.55-0.35 (m, 2H), 0.24-0.06 (m, 2H).

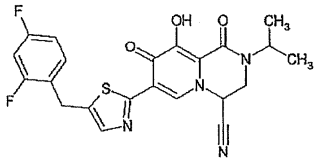
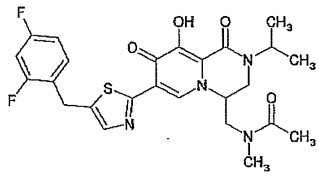
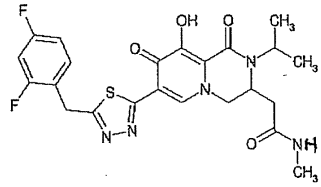
CUADRO 1-18

No.	Fórmula estructural	sal	^{1}H-NMR
72		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.69 (br s, 1H), 8.70 (s, 1H), 7.65 (s, 1H), 7.49-7.39 (m, 1H), 7.29-7.19 (m, 1H), 7.11-7.00 (m, 1H), 5.14-5.01 (m, 1H), 4.86-4.71 (m, 1H), 4.21 (s, 2H), 3.91-3.67 (m, 2H), 3.51-3.22 (m, 8H), 2.91 (d, 2H, J = 6.5 Hz), 1.14 (d, 3H, J = 6.7 Hz), 1.13 (d, 3H, J = 6.7 Hz).
73		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.69 (s, 1.0H), 7.65 (s, 1.0H), 7.49-7.40 (m, 1.0H), 7.29-7.19 (m, 1.0H), 7.11-7.02 (m, 1.0H), 5.13-5.03 (m, 1.0H), 4.84-4.72 (m, 1.0H), 4.21 (s, 2.0H), 3.88-3.55 (m, 2.0H), 3.55-3.25 (m, 4.0H), 3.15 (s, 1.5H), 3.12 (s, 1.5H), 3.02-2.82 (m, 2.0H), 2.88 (s, 1.5H), 2.79 (s, 1.5H), 1.13 (d, 6.0H, J = 6.5 Hz).
74		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.85 (s, 1H), 7.57-7.50 (m, 1H), 7.32-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.62-4.56 (m, 1H), 4.53-4.30 (m, 3H), 4.49 (s, 2H), 2.69-2.45 (m, 2H), 1.30 (d, 3H, J = 7.2 Hz), 1.28 (d, 3H, J = 7.2 Hz).
75		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.50 (s, 1H), 8.80 (s, 1H), 7.57-7.49 (m, 1H), 7.33-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.57-4.46 (m, 2H), 4.48 (s, 2H), 4.45-4.34 (m, 2H), 2.84 (s, 3H), 2.83 (s, 3H), 2.81-2.54 (m, 2H), 1.28 (d, 3H, J = 6.8 Hz), 1.25 (d, 3H, J = 6.8 Hz).

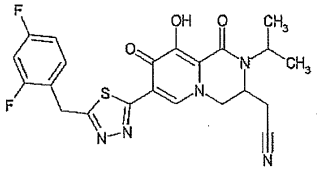
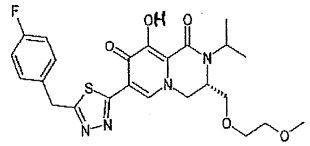
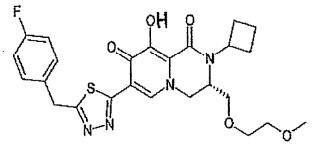
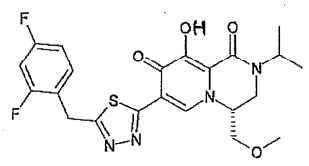
CUADRO 1-19

No.	Fórmula estructural	sal	^{1}H-NMR
76		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.81-12.55 (m, 1H), 8.70 (d, 1H, J = 3.7 Hz), 7.65 (s, 1H), 7.50-7.40 (m, 1H), 7.29-7.19 (m, 1H), 7.11-7.03 (m, 1H), 5.13-5.02 (m, 1H), 4.86-4.72 (m, 1H), 4.21 (s, 2H), 3.88-3.73 (m, 2H), 3.42-3.10 (m, 3H), 2.90-2.80 (m, 1H), 2.83 (s, 1.8H), 2.76 (s, 1.2H), 1.13 (d, 3H, J = 7.0 Hz), 1.12 (d, 3H, J = 6.7 Hz), 0.99 (t, 1.2H, J = 7.2 Hz), 0.93 (t, 1.8H, J = 7.4 Hz).
77		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.67 (br s, 1H), 8.68 (s, 1H), 7.65 (s, 1H), 7.50-7.40 (m, 1H), 7.29-7.19 (m, 1H), 7.12-7.03 (m, 1H), 5.14-5.04 (m, 1H), 4.85-4.73 (m, 1H), 4.21 (s, 2H), 3.90-3.76 (m, 2H), 3.35-3.10 (m, 4H), 2.84 (d, 2H, J = 6.7 Hz), 1.13 (t, 6H, J = 6.7 Hz), 0.98 (t, 3H, J = 7.4 Hz), 0.94 (t, 3H, J = 7.4 Hz).
78		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.66 (br s, 1H), 8.57 (s, 1H), 7.65 (s, 1H), 7.45 (td, 1H, J = 8.7, 6.6 Hz), 7.36 (dd, 1H, J = 6.7, 6.1 Hz), 7.24 (ddd, 1H, J = 10.4, 9.5, 2.8 Hz), 7.07 (tdd, 1H, J = 8.7, 2.8, 0.9 Hz), 4.75 (sep, 1H, J = 6.7 Hz), 4.71-4.63 (br m, 1H), 4.21 (s, 2H), 3.85 (dd, 1H, J = 13.8, 4.1 Hz), 3.75 (dd, 1H, J = 13.8, 1.2 Hz), 3.38 (ddd, 1H, J = 14.1, 6.1, 5.6 Hz), 3.16 (ddd, 1H, J = 14.1, 9.0, 6.7 Hz), 2.89 (s, 3H), 1.21 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).

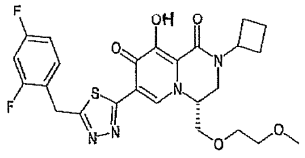
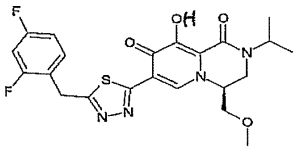
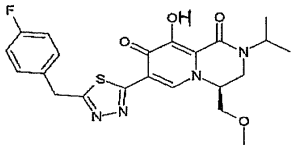
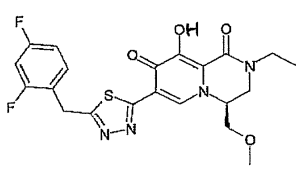
CUADRO 1-20

No.	Fórmula estructural	sal	^{1}H-NMR
79		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.94 (s, 1H), 7.70 (s, 1H), 7.47 (td, 1H, J = 8.6, 6.8 Hz), 7.25 (ddd, 1H, J = 10.1, 9.5, 2.6 Hz), 7.08 (tdd, 1H, J = 8.6, 2.6, 1.1 Hz), 6.30-6.25 (br m, 1H), 4.80 (sep, 1H, J = 6.8 Hz), 4.24 (dd, 1H, J = 14.1, 2.0 Hz), 4.23 (s, 2H), 4.02 (dd, 1H, J = 14.1, 3.5 Hz), 1.23 (d, 3H, J = 6.8 Hz), 1.16 (d, 3H, J = 6.8 Hz).
80		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.35 (s, 1H), 7.64 (s, 1H), 7.46 (td, 1H, J = 8.8, 7.1 Hz), 7.25 (ddd, 1H, J = 10.6, 9.5, 2.6 Hz), 7.08 (tdd, 1H, J = 8.8, 2.6, 1.3 Hz), 4.92-4.84 (br m, 1H), 4.78 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 3.87 (dd, 1H, J = 14.1, 4.4 Hz), 3.83 (dd, 1H, J = 14.1, 10.8 Hz), 3.71 (dd, 1H, J = 13.9, 1.1 Hz), 3.39 (dd, 1H, J = 13.9, 4.0 Hz), 2.90 (s, 3H), 1.77 (s, 3H), 1.19 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
81		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.42 (s, 1H), 8.80 (s, 1H), 7.92 (q, 1H, J = 4.4 Hz), 7.57-7.50 (m, 1H), 7.33-7.26 (m, 1H), 7.15-7.08 (m, 1H), 4.53-4.30 (m, 4H), 4.49 (s, 2H), 2.56 (d, 3H, J = 4.4 Hz), 2.44-2.37 (m, 2H), 1.29 (d, 3H, J = 6.8 Hz), 1.27 (d, 3H, J = 6.8 Hz).

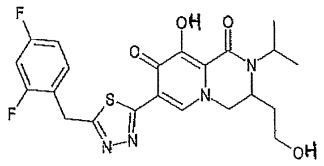
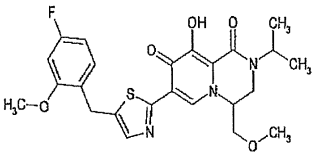
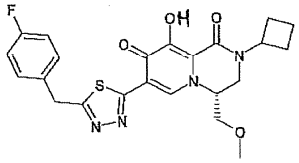
CUADRO 1-21

No.	Fórmula estructural	sal	^{1}H-NMR
82		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.88 (s, 1H), 7.58-7.50 (m, 1H), 7.32-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.64 (d, 1H, J = 13.2 Hz), 4.54-4.41 (m, 3H), 4.49 (s, 2H), 3.12 (dd, 1H, J = 17.5, 7.0 Hz), 3.01 (dd, 1H, J = 17.5, 4.2 Hz), 1.31 (d, 3H, J = 6.8 Hz), 1.31 (d, 3H, J = 6.8 Hz).
83		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.42 (br s, 1H), 8.82 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.14 (m, 2H), 4.68-4.62 (m, 1H), 4.55-4.42 (m, 1H), 4.47 (s, 2H), 4.36 (dd, 1H, J = 13.1, 3.6 Hz), 4.23-4.13 (m, 1H), 3.52-3.39 (m, 4H), 3.32-3.25 (m, 2H), 3.09 (s, 3H), 1.29 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).
84		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.48 (br s, 1H), 8.82 (s, 1H), 7.44-7.36 (m, 2H), 7.22-7.15 (m, 2H), 4.70-4.64 (m, 1H), 4.61-4.50 (m, 1H), 4.47 (s, 2H), 4.45-4.37 (m, 1H), 4.31-4.23 (m, 1H), 3.58-3.39 (m, 4H), 3.31-3.25 (m, 2H), 3.09 (s, 3H), 2.37-2.12 (m, 4H), 1.75-1.62 (m, 2H).
85		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.82 (s, 1H), 8.80 (s, 1H), 7.54 (td, 1H, J = 8.8, 6.7 Hz), 7.29 (ddd, 1H, J = 10.2, 9.3, 2.6 Hz), 7.12 (tdd, 1H, J = 8.8, 2.6 0.9 Hz), 5.01-4.93 (br m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 3.84 (dd, 1H, J = 13.9, 3.9 Hz), 3.75 (dd, 1H, J = 13.9, 1.4 Hz), 3.62 (dd, 1H, J = 10.2, 5.8 Hz), 3.57 (dd, 1H, J = 10.2, 7.7 Hz), 3.25 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).

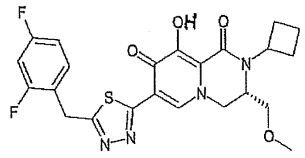
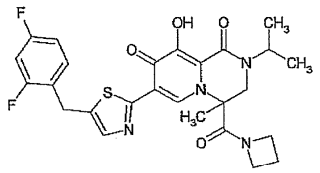
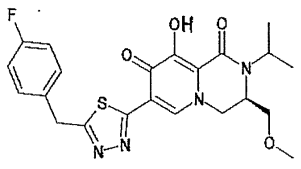
CUADRO 1-22

No.	Fórmula estructural	sal	^{1}H-NMR
86		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.73 (br s, 1H), 8.82 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 5.00–4.84 (m, 2H), 4.49 (s, 2H), 3.98–3.87 (m, 2H), 3.74 (dd, 1H, J = 10.4, 6.0 Hz), 3.64 (dd, 1H, J = 10.4, 7.4 Hz), 3.58–3.46 (m, 2H), 3.34 (t, 2H, J = 4.6 Hz), 3.12 (s, 3H), 2.34–2.03 (m, 4H), 1.76–1.65 (m, 2H).
87		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.80 (s, 1H), 7.59–7.49 (m, 1H), 7.35–7.24 (m, 1H), 7.16–7.07 (m, 1H), 5.01–4.93 (m, 1H), 4.77 (t, 1H, J = 6.7 Hz), 4.49 (s, 2H), 3.84 (dd, 1H, J = 13.7, 3.9 Hz), 3.75 (dd, 1H, J = 13.7, 2.5 Hz), 3.62 (dd, 1H, J = 10.2, 5.8 Hz), 3.57 (dd, 1H, J = 10.2, 7.7 Hz), 3.25 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
88		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.82 (br s, 1H), 8.80 (s, 1H), 7.45–7.39 (m, 2H), 7.22–7.15 (m, 2H), 5.01–4.94 (m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 3.84 (dd, 1H, J = 13.7, 3.9 Hz), 3.75 (dd, 1H, J = 13.7, 1.6 Hz), 3.62 (dd, 1H, J = 10.4, 5.8 Hz), 3.57 (dd, 1H, J = 10.4, 7.7 Hz), 3.25 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
89		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.76 (br s, 1H), 8.78 (s, 1H), 7.58–7.50 (m, 1H), 7.32–7.26 (m, 1H), 7.14–7.08 (m, 1H), 4.99–4.89 (m, 1H), 4.49 (s, 2H), 4.07 (dd, 1H, J = 13.7, 4.4 Hz), 3.74–3.56 (m, 4H), 3.44–3.33 (m, 1H), 3.25 (s, 3H), 1.14 (t, 3H, J = 7.2 Hz).

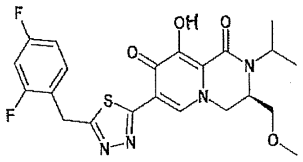
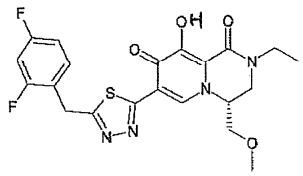
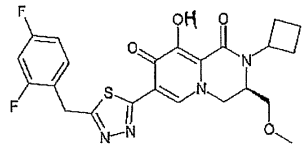
CUADRO 1-23

No.	Fórmula estructural	sal	^{1}H-NMR
90		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.47 (s, 1H), 8.87 (s, 1H), 7.57–7.49 (m, 1H), 7.32–7.24 (m, 1H), 7.15–7.07 (m, 1H), 4.66 (dd, 1H, J = 13.5, 1.7 Hz), 4.53 (sep, 1H, J = 6.8 Hz), 4.49 (s, 2H), 4.35–4.28 (m, 1H), 4.14–4.07 (m, 1H), 3.62–3.47 (m, 2H), 1.81–1.51 (m, 2H), 1.29 (d, 6H, J = 6.8 Hz).
91		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.76–12.55 (br m, 1H), 8.61 (s, 1H), 7.61 (s, 1H), 7.25 (dd, 1H, J = 8.5, 6.9 Hz), 6.92 (dd, 1H, J = 11.3, 2.4 Hz), 6.73 (td, 1H, J = 8.5, 2.4 Hz), 4.94–4.86 (br m, 1H), 4.77 (sep, 1H, J = 6.9 Hz), 4.09 (s, 2H), 3.84–3.79 (m, 1H), 3.83 (s, 3H), 3.76–3.69 (m, 1H), 3.60 (dd, 1H, J = 10.5, 5.6 Hz), 3.54 (dd, 1H, J = 10.5, 7.7 Hz), 3.23 (s, 3H), 1.16 (d, 3H, J = 6.9 Hz), 1.15 (d, 3H, J = 6.9 Hz).
92		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.70 (br s, 1H), 8.81 (s, 1H), 7.45–7.38 (m, 2H), 7.22–7.15 (m, 2H), 5.02–4.85 (m, 2H), 4.47 (s, 2H), 3.98–3.87 (m, 2H), 3.65 (dd, 1H, J = 10.3, 5.8 Hz), 3.57 (dd, 1H, J = 10.3, 7.5 Hz), 3.25 (s, 3H), 2.31–2.04 (m, 4H), 1.77–1.65 (m, 2H).

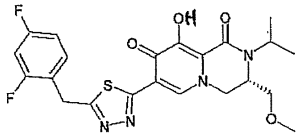
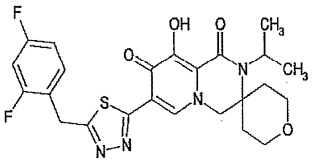
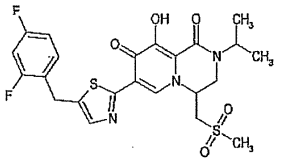
CUADRO 1-24

No.	Fórmula estructural	sal	^{1}H-NMR
93		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.84 (s, 1H), 7.57–7.49 (m, 1H), 7.32–7.25 (m, 1H), 7.15–7.07 (m, 1H), 4.68 (d, 1H, J = 13.2 Hz), 4.60–4.49 (m, 1H), 4.48 (s, 2H), 4.41 (dd, 1H, J = 13.2, 3.7 Hz), 4.32–4.25 (m, 1H), 3.43 (dd, 1H, J = 10.4, 4.6 Hz), 3.39 (dd, 1H, J = 10.4, 6.8 Hz), 3.21 (s, 3H), 2.39–2.11 (m, 4H), 1.77–1.63 (m, 2H).
94		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.79 (br s, 1H), 8.60 (s, 1H), 7.67 (s, 1H), 7.45 (td, 1H, J = 8.2, 6.0 Hz), 7.24 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.07 (tdd, 1H, J = 8.2, 2.6, 0.9 Hz), 4.70 (sep, 1H, J = 6.7 Hz), 4.22 (s, 2H), 4.19–4.14 (br m, 1H), 4.09 (d, 1H, J = 14.1 Hz), 4.00 (d, 1H, J = 14.1 Hz), 3.88–3.81 (br m, 2H), 3.74–3.69 (br m, 1H), 2.14–2.04 (br m, 2H), 1.94 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.13 (d, 3H, J = 6.7 Hz).
95		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.84 (s, 1H), 7.43–7.38 (m, 2H), 7.21–7.14 (m, 2H), 4.66 (d, 1H, J = 13.2 Hz), 4.47 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 4.34 (dd, 1H, J = 13.5, 3.7 Hz), 4.22–4.17 (m, 1H), 3.49 (dd, 1H, J = 10.6, 4.3 Hz), 3.39 (dd, 1H, J = 10.6, 7.5 Hz), 3.21 (s, 3H), 1.30 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).

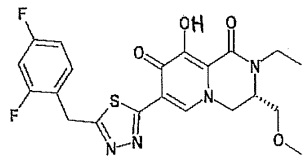
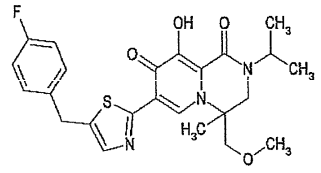
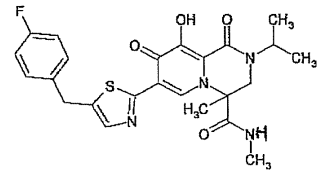
CUADRO 1-25

No.	Fórmula estructural	sal	^{1}H-NMR
96		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.45 (br s, 1H), 8.84 (s, 1H), 7.58-7.50 (m, 1H), 7.33-7.25 (m, 1H), 7.15-7.07 (m, 1H), 4.66 (dd, 1H, J = 13.4, 1.6 Hz), 4.49 (s, 2H), 4.47 (sep, 1H, J = 6.8 Hz), 4.35 (dd, 1H, J = 13.4, 3.7 Hz), 4.23-4.17 (m, 1H), 3.49 (dd, 1H, J = 10.2, 4.2 Hz), 3.39 (dd, 1H, J = 10.2, 7.4 Hz), 3.21 (s, 3H), 1.30 (d, 3H, J = 6.8 Hz), 1.28 (d, 3H, J = 6.8 Hz).
97		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.76 (br s, 1H), 8.78 (s, 1H), 7.58-7.50 (m, 1H), 7.32-7.26 (m, 1H), 7.14-7.08 (m, 1H), 4.99-4.89 (m, 1H), 4.49 (s, 2H), 4.07 (dd, 1H, J = 13.7, 4.4 Hz), 3.74-3.56 (m, 4H), 3.44-3.33 (m, 1H), 3.25 (s, 3H), 1.14 (t, 3H, J = 7.2 Hz).
98		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.51 (br s, 1H), 8.84 (s, 1H), 7.58-7.49 (m, 1H), 7.33-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.71-4.64 (m, 1H), 4.60-4.46 (m, 3H), 4.41 (dd, 1H, J = 13.7, 3.9 Hz), 4.31-4.25 (m, 1H), 3.46-3.36 (m, 2H), 3.21 (s, 3H), 2.37-2.12 (m, 4H), 1.77-1.64 (m, 2H).

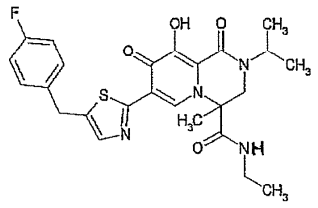
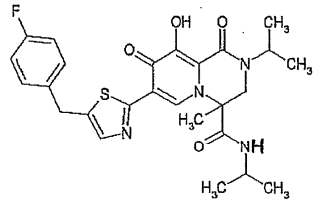
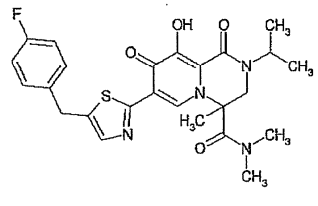
CUADRO 1-26

No.	Fórmula estructural	sal	^{1}H-NMR
99		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.46 (br s, 1H), 8.84 (s, 1H), 7.57-7.50 (m, 1H), 7.32-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.66 (dd, 1H, J = 13.2, 1.6 Hz), 4.52-4.42 (m, 1H), 4.49 (s, 2H), 4.35 (dd, 1H, J = 13.2, 4.0 Hz), 4.23-4.17 (m, 1H), 3.49 (dd, 1H, J = 10.4, 4.3 Hz), 3.39 (dd, 1H, J = 10.4, 7.5 Hz), 3.21 (s, 3H), 1.30 (d, 3H, J = 6.8 Hz), 1.28 (d, 3H, J = 6.8 Hz).
100		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.56 (br s, 1H), 9.02 (s, 1H), 7.53 (td, 1H, J = 8.5, 6.4 Hz), 7.29 (ddd, 1H, J = 10.5, 9.7, 2.4 Hz), 7.12 (tdd, 1H, J = 8.5, 2.4, 1.2 Hz), 4.72 (s, 2H), 4.49 (s, 2H), 4.16-4.02 (br m, 1H), 3.82-3.78 (m, 2H), 3.74-3.66 (m, 2H), 2.21-2.13 (m, 2H), 1.64-1.58 (m, 2H), 1.43 (d, 6H, J = 6.4 Hz).
101		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.66 (br s, 1H), 8.66 (s, 1H), 7.66 (s, 1H), 7.51-7.40 (m, 1H), 7.29-7.20 (m, 1H), 7.11-7.03 (m, 1H), 5.45-5.34 (m, 1H), 4.83-4.70 (m, 1H), 4.21 (s, 2H), 3.95-3.85 (m, 2H), 3.81-3.59 (m, 2H), 3.05 (s, 3H), 1.20 (d, 3H, J = 6.7 Hz), 1.14 (d, 3H, J = 6.7 Hz).

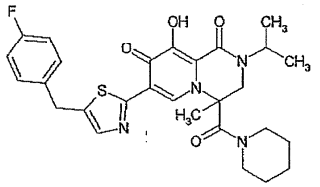
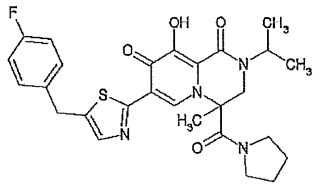
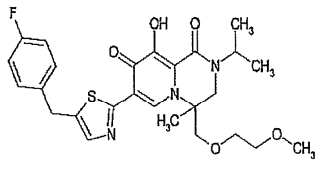
CUADRO 1-27

No.	Fórmula estructural	sal	^{1}H-NMR
102		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.50 (br s, 1H), 8.83 (s, 1H), 7.57-7.50 (m, 1H), 7.33-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.64 (dd, 1H, J = 13.7, 1.6 Hz), 4.49 (s, 2H), 4.43 (dd, 1H, J = 13.7, 4.1 Hz), 4.17-4.12 (m, 1H), 3.86 (dq, 1H, J = 13.4, 7.0 Hz), 3.54 (dd, 1H, J = 10.2, 5.1 Hz), 3.50 (dd, 1H, J = 10.2, 6.3 Hz), 3.27 (dq, 1H, J = 13.4, 7.0 Hz), 3.21 (s, 3H), 1.18 (t, 3H, J = 7.0 Hz).
103		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.61 (s, 1H), 7.70 (s, 1H), 7.36-7.29 (m, 2H), 7.18-7.11 (m, 2H), 4.80 (sep, 1H, J = 6.7 Hz), 4.20 (s, 2H), 3.74 (d, 1H, J = 13.7 Hz), 3.64 (d, 1H, J = 10.4 Hz), 3.64 (d, 1H, J = 13.7 Hz), 3.58 (d, 1H, J = 10.4 Hz), 3.24 (s, 3H), 1.63 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz).
104		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.79 (br s, 1H), 8.53 (s, 1H), 8.14 (q, 1H, J = 4.4 Hz), 7.69 (s, 1H), 7.36-7.30 (m, 2H), 7.18-7.11 (m, 2H), 4.70 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.09 (d, 1H, J = 13.9 Hz), 3.77 (d, 1H, J = 13.9 Hz), 2.60 (d, 3H, J = 4.4 Hz), 1.93 (s, 3H), 1.14 (d, 3H, J = 6.7 Hz), 1.09 (d, 3H, J = 6.7 Hz).

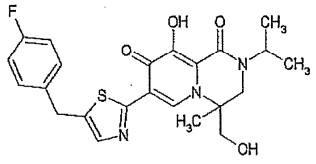
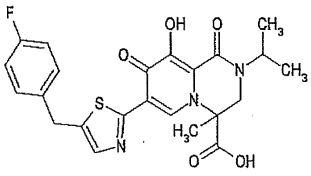
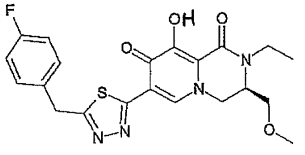
CUADRO 1-28

No.	Fórmula estructural	sal	^{1}H-NMR
105		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (br s, 1H), 8.52 (s, 1H), 8.18 (t, 1H, J = 5.2 Hz), 7.68 (s, 1H), 7.36–7.30 (m, 2H), 7.18–7.11 (m, 2H), 4.71 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.11 (d, 1H, J = 13.9 Hz), 3.78 (d, 1H, J = 13.9 Hz), 3.18–2.98 (m, 2H), 1.92 (s, 3H), 1.15 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz), 1.00 (t, 3H, J = 7.2 Hz).
106		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.84 (br s, 1H), 8.50 (s, 1H), 8.07 (d, 1H, J = 7.4 Hz), 7.68 (s, 1H), 7.36–7.30 (m, 2H), 7.18–7.11 (m, 2H), 4.72 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.16 (d, 1H, J = 14.1 Hz), 3.81 (sep, 1H, J = 6.7 Hz), 3.79 (d, 1H, J = 14.1 Hz), 1.93 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.15 (d, 3H, J = 6.7 Hz), 1.07 (d, 3H, J = 6.7 Hz), 1.06 (d, 3H, J = 6.7 Hz).
107		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.85 (s, 1H), 8.43 (s, 1H), 7.69 (s, 1H), 7.37–7.29 (m, 2H), 7.19–7.11 (m, 2H), 4.73 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.12 (d, 1H, J = 14.1 Hz), 3.79 (d, 1H, J = 14.1 Hz), 2.93 (s, 6H), 1.98 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz).

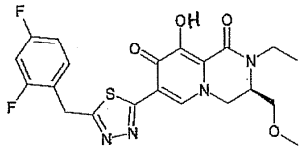
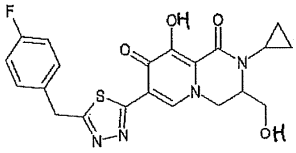
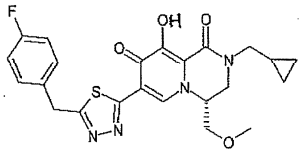
CUADRO 1-29

No.	Fórmula estructural	sal	^{1}H-NMR
108		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.96 (br s, 1H), 8.39 (s, 1H), 7.69 (s, 1H), 7.37–7.30 (m, 2H), 7.19–7.11 (m, 2H), 4.75 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.03 (d, 1H, J = 14.4 Hz), 3.80 (d, 1H, J = 14.4 Hz), 3.56–3.37 (br m, 4H), 1.90 (s, 3H), 1.59–1.50 (br m, 2H), 1.50–1.41 (br m, 4H), 1.18 (d, 3H, J = 6.7 Hz), 1.14 (d, 3H, J = 6.7 Hz).
109		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.79 (br s, 1H), 8.54 (s, 1H), 7.69 (s, 1H), 7.37–7.30 (m, 2H), 7.19–7.11 (m, 2H), 4.70 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.12 (d, 1H, J = 14.1 Hz), 3.75 (d, 1H, J = 14.1 Hz), 3.65–3.53 (br m, 1H), 3.43–3.33 (br m, 1H), 3.33–3.23 (br m, 1H), 3.16–3.05 (br m, 1H), 2.01 (s, 3H), 1.94–1.84 (br m, 1H), 1.81–1.56 (br m, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.7 Hz).
110		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.12 (s, 1H), 8.63 (s, 1H), 7.69 (s, 1H), 7.36–7.30 (m, 2H), 7.18–7.11 (m, 2H), 4.79 (sep, 1H, J = 6.7 Hz), 4.20 (s, 2H), 3.74 (d, 1H, J = 10.2 Hz), 3.73 (d, 1H, J = 13.9 Hz), 3.66 (d, 1H, J = 10.2 Hz), 3.65 (d, 1H, J = 13.9 Hz), 3.54–3.42 (m, 2H), 3.38–3.30 (m, 2H), 3.11 (s, 3H), 1.63 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz).

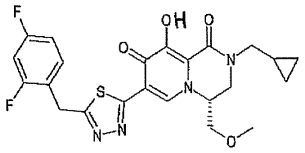
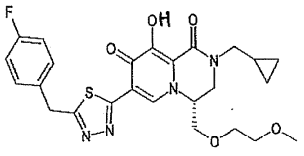
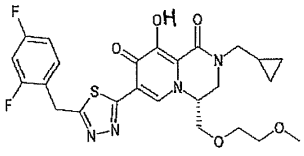
CUADRO 1-30

No.	Fórmula estructural	sal	^{1}H-NMR
111		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.14 (s, 1H), 8.63 (s, 1H), 7.69 (s, 1H), 7.36-7.30 (m, 2H), 7.18-7.11 (m, 2H), 4.79 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 3.72 (d, 1H, J = 13.7 Hz), 3.64 (d, 1H, J = 13.7 Hz), 3.61 (s, 2H), 1.59 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz).
112		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.87 (br s, 1H), 8.61 (s, 1H), 7.70 (s, 1H), 7.37-7.30 (m, 2H), 7.18-7.11 (m, 2H), 4.73 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.06 (d, 1H, J = 13.7 Hz), 3.80 (d, 1H, J = 13.7 Hz), 1.98 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.14 (d, 3H, J = 6.7 Hz).
113		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.64-12.34 (m, 1H), 8.83 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.14 (m, 2H), 4.64 (dd, 1H, J = 13.4, 1.5 Hz), 4.47 (s, 2H), 4.42 (dd, 1H, J = 13.4, 4.4 Hz), 4.17-4.11 (m, 1H), 3.86 (dq, 1H, J = 14.0, 7.0 Hz), 3.54 (dd, 1H, J = 10.4, 4.9 Hz), 3.50 (dd, 1H, J = 10.4, 6.3 Hz), 3.27 (dq, 1H, J = 14.0, 7.0 Hz), 3.22 (s, 3H), 1.20 (t, 3H, J = 7.0 Hz).

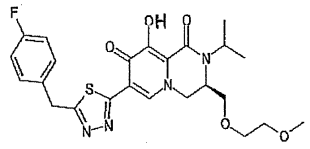
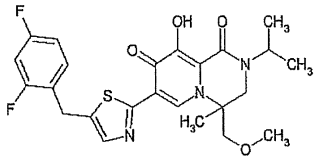
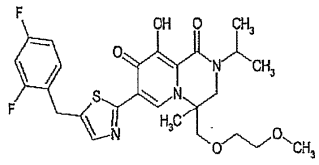
CUADRO 1-31

No.	Fórmula estructural	sal	^{1}H-NMR
114		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.50 (br s, 1H), 8.83 (s, 1H), 7.57–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.64 (dd, 1H, J = 13.7, 1.6 Hz), 4.49 (s, 2H), 4.43 (dd, 1H, J = 13.7, 4.1 Hz), 4.17–4.12 (m, 1H), 3.86 (dq, 1H, J = 13.4, 7.0 Hz), 3.54 (dd, 1H, J = 10.2, 5.1 Hz), 3.50 (dd, 1H, J = 10.2, 6.3 Hz), 3.27 (dq, 1H, J = 13.4, 7.0 Hz), 3.21 (s, 3H), 1.18 (t, 3H, J = 7.0 Hz).
115		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.72 (br s, 1H), 8.79 (s, 1H), 7.44–7.37 (m, 2H), 7.22–7.15 (m, 2H), 4.61 (dd, 1H, J = 13.6, 1.6 Hz), 4.47 (s, 2H), 4.35 (dd, 1H, J = 13.6, 4.2 Hz), 3.86–3.80 (m, 1H), 3.62 (dd, 1H, J = 11.5, 3.8 Hz), 3.52 (dd, 1H, J = 11.5, 7.1 Hz), 2.95–2.88 (m, 1H), 1.03–0.94 (m, 1H), 0.90–0.83 (m, 1H), 0.83–0.72 (m, 2H).
116		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (s, 1H), 8.79 (s, 1H), 7.46–7.38 (m, 2H), 7.24–7.15 (m, 2H), 5.02–4.90 (m, 1H), 4.47 (s, 2H), 4.12 (dd, 1H, J = 13.7, 3.9 Hz), 3.87–3.79 (m, 1H), 3.73–3.58 (m, 2H), 3.45 (dd, 1H, J = 14.0, 7.3 Hz), 3.31 (dd, 1H, J = 14.0, 6.8 Hz), 3.26 (s, 3H), 1.15–1.03 (m, 1H), 0.58–0.46 (m, 2H), 0.39–0.26 (m, 2H).

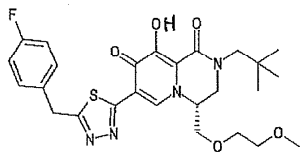
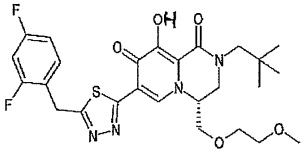
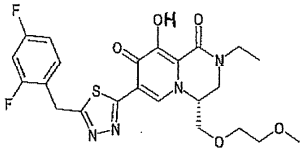
CUADRO 1-32

No.	Fórmula estructural	sal	^{1}H-NMR
117		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (br s, 1H), 8.79 (s, 1H), 7.59–7.50 (m, 1H), 7.33–7.26 (m, 1H), 7.15–7.08 (m, 1H), 4.99–4.92 (m, 1H), 4.49 (s, 2H), 4.12 (dd, 1H, J = 13.8, 4.3 Hz), 3.87–3.80 (m, 1H), 3.69 (dd, 1H, J = 10.4, 5.6 Hz), 3.62 (dd, 1H, J = 10.4, 7.9 Hz), 3.45 (dd, 1H, J = 13.8, 7.3 Hz), 3.31 (dd, 1H, J = 13.9, 7.0 Hz), 3.26 (s, 3H), 1.14–1.03 (m, 1H), 0.57–0.46 (m, 2H), 0.39–0.27 (m, 2H).
118		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.76 (s, 1H), 8.80 (s, 1H), 7.45–7.38 (m, 2H), 7.23–7.15 (m, 2H), 4.96–4.89 (m, 1H), 4.47 (s, 2H), 4.11 (dd, 1H, J = 13.7, 4.2 Hz), 3.84 (dd, 1H, J = 13.7, 1.2 Hz), 3.78 (dd, 1H, J = 10.5, 5.6 Hz), 3.70 (dd, 1H, J = 10.5, 7.7 Hz), 3.59–3.39 (m, 3H), 3.37–3.29 (m, 3H), 3.10 (s, 3H), 1.13–1.04 (m, 1H), 0.58–0.46 (m, 2H), 0.38–0.27 (m, 2H).
119		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (br s, 1H), 8.80 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.16–7.08 (m, 1H), 4.97–4.89 (m, 1H), 4.49 (s, 2H), 4.12 (dd, 1H, J = 13.7, 4.4 Hz), 3.84 (dd, 1H, J = 13.7, 1.2 Hz), 3.78 (dd, 1H, J = 10.5, 5.6 Hz), 3.70 (dd, 1H, J = 10.5, 7.7 Hz), 3.59–3.40 (m, 3H), 3.37–3.29 (m, 3H), 3.10 (s, 3H), 1.14–1.04 (m, 1H), 0.58–0.47 (m, 2H), 0.38–0.27 (m, 2H).

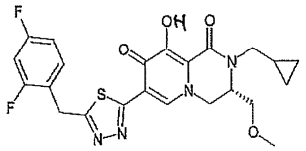
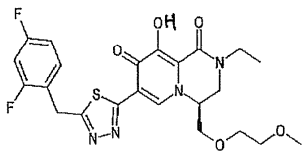
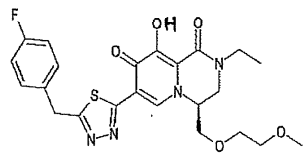
CUADRO 1-33

No.	Fórmula estructural	sal	^{1}H-NMR
120		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.42 (br s, 1H), 8.82 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.14 (m, 2H), 4.65 (d, 1H, J = 12.5 Hz), 4.55-4.42 (m, 1H), 4.47 (s, 2H), 4.36 (dd, 1H, J = 13.1, 3.6 Hz), 4.23-4.13 (m, 1H), 3.52-3.39 (m, 4H), 3.32-3.25 (m, 2H), 3.09 (s, 3H), 1.29 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).
121		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.10 (br s, 1H), 8.58 (s, 1H), 7.66 (s, 1H), 7.44 (td, 1H, J = 8.7, 6.7 Hz), 7.23 (ddd, 1H, J = 10.4, 9.5, 2.6 Hz), 7.06 (tdd, 1H, J = 8.7, 2.6, 0.9 Hz), 4.78 (sep, 1H, J = 6.7 Hz), 4.20 (s, 2H), 3.73 (d, 1H, J = 13.9 Hz), 3.63 (d, 1H, J = 13.9 Hz), 3.63 (d, 1H, J = 10.2 Hz), 3.56 (d, 1H, J = 10.2 Hz), 3.22 (s, 3H), 1.61 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
122		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.12 (br s, 1H), 8.62 (s, 1H), 7.67 (s, 1H), 7.45 (td, 1H, J = 8.8, 7.0 Hz), 7.25 (ddd, 1H, J = 10.4, 9.3, 2.6 Hz), 7.07 (tdd, 1H, J = 8.8, 2.6, 1.0 Hz), 4.79 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 3.78-3.70 (m, 2H), 3.66 (d, 1H, J = 10.2 Hz), 3.65 (d, 1H, J = 13.9 Hz), 3.54-3.42 (m, 2H), 3.37-3.29 (m, 2H), 3.11 (s, 3H), 1.63 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz).

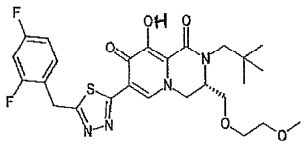
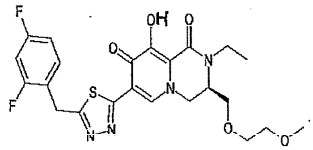
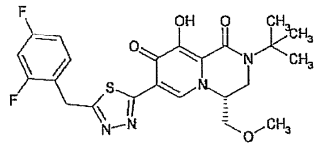
CUADRO 1-34

No.	Fórmula estructural	sal	^{1}H-NMR
123		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.78 (s, 1H), 8.82 (s, 1H), 7.45–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.93–4.86 (m, 1H), 4.47 (s, 2H), 4.19 (dd, 1H, J = 13.7, 4.2 Hz), 3.82 (dd, 1H, J = 10.4, 5.6 Hz), 3.78–3.70 (m, 2H), 3.58–3.47 (m, 2H), 3.42 (d, 1H, J = 13.4 Hz), 3.35–3.31 (m, 2H), 3.23 (d, 1H, J = 13.4 Hz), 3.11 (s, 3H), 0.98 (s, 9H).
124		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.78 (br s, 1H), 8.80 (s, 1H), 7.57–7.50 (m, 1H), 7.32–7.24 (m, 1H), 7.14–7.07 (m, 1H), 4.92–4.85 (m, 1H), 4.48 (s, 2H), 4.18 (dd, 1H, J = 13.7, 4.2 Hz), 3.81 (dd, 1H, J = 10.6, 5.7 Hz), 3.76–3.69 (m, 2H), 3.56–3.46 (m, 2H), 3.41 (d, 1H, J = 13.4 Hz), 3.34–3.30 (m, 2H), 3.22 (d, 1H, J = 13.4 Hz), 3.09 (s, 3H), 0.97 (s, 9H).
125		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.78 (br s, 1H), 8.79 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.96–4.88 (m, 1H), 4.49 (s, 2H), 4.07 (dd, 1H, J = 13.6, 4.3 Hz), 3.79–3.59 (m, 4H), 3.57–3.45 (m, 2H), 3.45–3.36 (m, 1H), 3.33 (t, 2H, J = 4.6 Hz), 3.10 (s, 3H), 1.15 (t, 3H, J = 7.2 Hz).

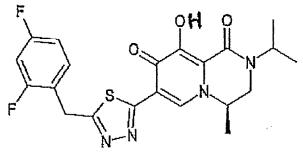
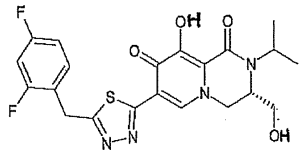
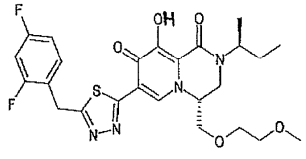
CUADRO 1-35

No.	Fórmula estructural	sal	^{1}H-NMR
126		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.47 (br s, 1H), 8.83 (s, 1H), 7.56–7.49 (m, 1H), 7.32–7.24 (m, 1H), 7.14–7.07 (m, 1H), 4.66 (dd, 1H, J = 13.4, 1.6 Hz), 4.48 (s, 2H), 4.44 (dd, 1H, J = 13.4, 4.2 Hz), 4.25–4.20 (m, 1H), 3.68 (dd, 1H, J = 14.0, 7.0 Hz), 3.57 (dd, 1H, J = 10.2, 4.6 Hz), 3.50 (dd, 1H, J = 10.2, 6.5 Hz), 3.20 (dd, 1H, J = 14.0, 7.0 Hz), 3.20 (s, 3H), 1.20–1.09 (m, 1H), 0.58–0.46 (m, 2H), 0.43–0.35 (m, 1H), 0.35–0.27 (m, 1H).
127		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.78 (br s, 1H), 8.79 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.96–4.88 (m, 1H), 4.49 (s, 2H), 4.07 (dd, 1H, J = 13.6, 4.3 Hz), 3.79–3.59 (m, 4H), 3.57–3.45 (m, 2H), 3.45–3.36 (m, 1H), 3.33 (t, 2H, J = 4.6 Hz), 3.10 (s, 3H), 1.15 (t, 3H, J = 7.2 Hz).
128		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.77 (br s, 1H), 8.80 (s, 1H), 7.44–7.39 (m, 2H), 7.22–7.15 (m, 2H), 4.95–4.88 (m, 1H), 4.47 (s, 2H), 4.07 (dd, 1H, J = 13.6, 4.3 Hz), 3.78–3.60 (m, 4H), 3.57–3.46 (m, 2H), 3.43–3.37 (m, 1H), 3.33 (t, 2H, J = 4.6 Hz), 3.10 (s, 3H), 1.15 (t, 3H, J = 7.2 Hz).

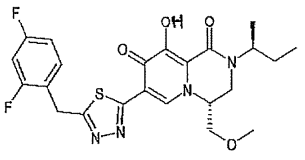
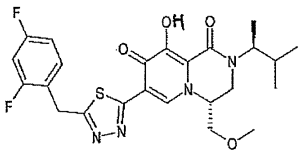
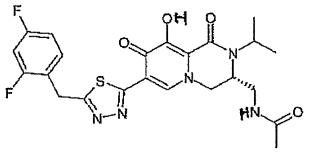
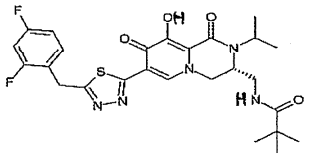
CUADRO 1-36

No.	Fórmula estructural	sal	^{1}H-NMR
129		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.67 (s, 1H), 8.83 (s, 1H), 7.59-7.49 (m, 1H), 7.34-7.25 (m, 1H), 7.16-7.07 (m, 1H), 4.70-4.55 (m, 2H), 4.49 (s, 2H), 4.03-3.97 (br m, 1H), 3.95 (d, 1H, J = 13.4 Hz), 3.66-3.59 (m, 2H), 3.47-3.41 (m, 2H), 3.27-3.22 (m, 2H), 3.07 (s, 3H), 2.85 (d, 1H, J = 13.4 Hz), 0.98 (s, 9H).
130		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.50 (s, 1H), 8.80 (s, 1H), 7.59-7.49 (m, 1H), 7.34-7.25 (m, 1H), 7.15-7.07 (m, 1H), 4.68-4.59 (m, 1H), 4.48 (s, 2H), 4.43 (dd, 1H, J = 13.4, 4.2 Hz), 4.17-4.09 (m, 1H), 3.86 (td, 1H, J = 13.9, 7.0 Hz), 3.67-3.56 (m, 2H), 3.52-3.41 (m, 2H), 3.34-3.22 (m, 3H), 3.09 (s, 3H), 1.20 (t, 3H, J = 7.0 Hz).
131		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.97-12.84 (br m, 1H), 8.76 (s, 1H), 7.58-7.50 (m, 1H), 7.33-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.92-4.85 (br m, 1H), 4.48 (s, 2H), 3.98-3.84 (m, 2H), 3.67 (dd, 1H, J = 10.1, 5.6 Hz), 3.59 (dd, 1H, J = 10.1, 7.7 Hz), 3.28 (s, 3H), 1.48 (s, 9H).

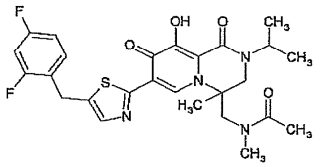
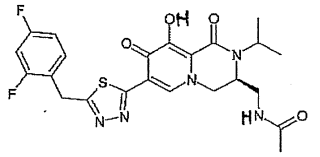
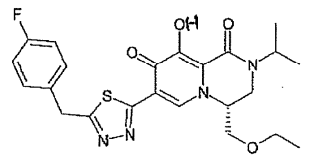
CUADRO 1-37

No.	Fórmula estructural	sal	^{1}H-NMR
132		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.79 (br s, 1H), 8.90 (s, 1H), 7.58-7.50 (m, 1H), 7.33-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.97-4.88 (m, 1H), 4.84-4.74 (m, 1H), 4.49 (s, 2H), 3.81 (dd, 1H, J = 13.5, 3.7 Hz), 3.63 (dd, 1H, J = 13.5, 2.2 Hz), 1.39 (d, 3H, J = 6.6 Hz), 1.19 (d, 3H, J = 6.8 Hz), 1.16 (d, 3H, J = 6.8 Hz).
133		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.48 (s, 1H), 8.80 (s, 1H), 7.57-7.50 (m, 1H), 7.32-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.67 (d, 1H, J = 13.1 Hz), 4.51 (sep, 1H, J = 6.8 Hz), 4.49 (s, 2H), 4.34 (dd, 1H, J = 13.1, 3.7 Hz), 4.00-3.93 (m, 1H), 3.57 (dd, 1H, J = 11.4, 3.7 Hz), 3.37 (dd, 1H, J = 11.4, 8.3 Hz), 1.29 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).
134		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.88 (br s, 1H), 8.83-8.80 (m, 1H), 7.59-7.50 (m, 1H), 7.33-7.24 (m, 1H), 7.16-7.08 (m, 1H), 5.01-4.90 (br m, 1H), 4.60-4.50 (m, 1H), 4.49 (s, 2H), 3.87-3.63 (m, 4H), 3.57-3.46 (m, 2H), 3.35-3.30 (m, 2H), 3.12-3.10 (m, 3H), 1.59-1.48 (m, 2H), 1.15 (d, 3H, J = 6.7 Hz), 0.91-0.78 (m, 3H).

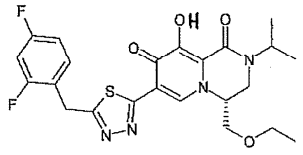
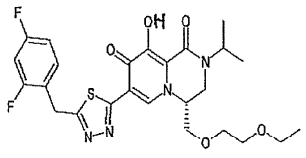
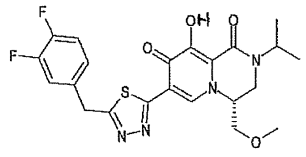
CUADRO 1-38

No.	Fórmula estructural	sal	^{1}H-NMR
135		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.89 (br s, 1H), 8.81 (s, 1H), 7.59-7.50 (m, 1H), 7.34-7.25 (m, 1H), 7.16-7.06 (m, 1H), 5.03-4.92 (br m, 1H), 4.59-4.50 (m, 1H), 4.49 (s, 2H), 3.73-3.54 (m, 4H), 3.26-3.23 (m, 3H), 1.61-1.45 (m, 2H), 1.15 (d, 3H, J = 6.7 Hz), 0.91-0.80 (m, 3H),
136		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.96 (br s, 1H), 8.82 (s, 1H), 7.59-7.49 (m, 1H), 7.35-7.24 (m, 1H), 7.17-7.06 (m, 1H), 5.04-4.91 (m, 1H), 4.49 (s, 2H), 4.30-3.57 (m, 5H), 3.27-3.22 (m, 3H), 1.87-1.69 (m, 1H), 1.17 (d, 3H, J = 6.8 Hz), 0.97-0.79 (m, 6H).
137		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.42 (br s, 1H), 8.71 (s, 1H), 8.23-8.17 (m, 1H), 7.58-7.50 (m, 1H), 7.33-7.26 (m, 1H), 7.15-7.08 (m, 1H), 4.58 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.43 (dd, 1H, J = 13.0, 1.3 Hz), 4.31 (dd, 1H, J = 13.0, 3.0 Hz), 3.97-3.91 (m, 1H), 3.45-3.36 (m, 1H), 2.97-2.86 (m, 1H), 1.80 (s, 3H), 1.34 (d, 3H, J = 6.7 Hz), 1.27 (d, 3H, J = 6.7 Hz).
138		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.49 (br s, 1H), 8.72 (s, 1H), 7.88-7.83 (m, 1H), 7.57-7.50 (m, 1H), 7.32-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.57 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.38-4.28 (m, 2H), 3.99-3.92 (m, 1H), 3.38-3.29 (m, 1H), 3.04-2.95 (m, 1H), 1.38 (d, 3H, J = 6.7 Hz), 1.29 (d, 3H, J = 6.7 Hz), 1.08 (s, 9H).

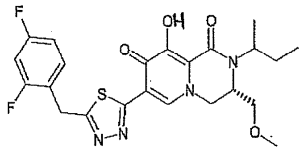
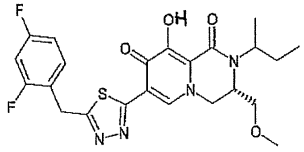
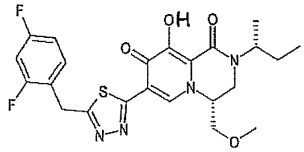
CUADRO 1-39

No.	Fórmula estructural	sal	^{1}H-NMR
139		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.18 (br s, 1H), 8.47 (s, 1H), 7.67 (s, 1H), 7.46 (td, 1H, J = 8.8, 6.6 Hz), 7.25 (ddd, 1H, J = 10.4, 9.3, 2.6 Hz), 7.08 (tdd, 1H, J = 8.8, 2.6, 0.9 Hz), 4.79 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 3.79 (d, 1H, J = 13.9 Hz), 3.74 (d, 1H, J = 14.6 Hz), 3.68 (d, 1H, J = 13.9 Hz), 3.57 (d, 1H, J = 14.6 Hz), 2.75 (s, 3H), 1.81 (s, 3H), 1.67 (s, 3H), 1.22 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz).
140		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.42 (br s, 1H), 8.71 (s, 1H), 8.22–8.17 (m, 1H), 7.57–7.50 (m, 1H), 7.33–7.26 (m, 1H), 7.15–7.08 (m, 1H), 4.58 (sep, 1H, J = 6.8 Hz), 4.49 (s, 2H), 4.43 (d, 1H, J = 13.0 Hz), 4.30 (dd, 1H, J = 13.0, 3.0 Hz), 3.98–3.91 (m, 1H), 2.96–2.86 (m, 1H), 2.56–2.50 (m, 1H), 1.80 (s, 3H), 1.34 (d, 3H, J = 6.8 Hz), 1.27 (d, 3H, J = 6.8 Hz).
141		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.84 (s, 1H), 8.82 (s, 1H), 7.45–7.38 (m, 2H), 7.23–7.15 (m, 2H), 4.99–4.91 (m, 1H), 4.77 (sep, 1H, J = 6.8 Hz), 4.47 (s, 2H), 3.84 (dd, 1H, J = 13.8, 4.1 Hz), 3.75 (dd, 1H, J = 13.8, 1.7 Hz), 3.66 (dd, 1H, J = 10.4, 6.0 Hz), 3.59 (dd, 1H, J = 10.4, 7.5 Hz), 3.50–3.34 (m, 2H), 1.17 (d, 3H, J = 6.8 Hz), 1.16 (d, 3H, J = 6.8 Hz), 1.02 (t, 3H, J = 7.1 Hz).

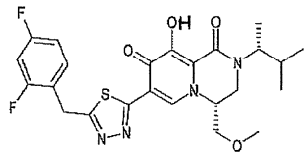
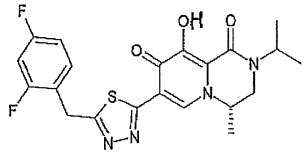
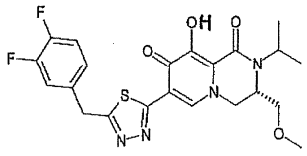
CUADRO 1-40

No.	Fórmula estructural	sal	^{1}H-NMR
142		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.83 (br s, 1H), 8.81 (s, 1H), 7.58-7.51 (m, 1H), 7.33-7.25 (m, 1H), 7.15-7.07 (m, 1H), 4.98-4.91 (m, 1H), 4.77 (sep, 1H, J = 6.8 Hz), 4.49 (s, 2H), 3.84 (dd, 1H, J = 13.7, 4.0 Hz), 3.78-3.73 (m, 1H), 3.69-3.56 (m, 2H), 3.50-3.34 (m, 2H), 1.17 (d, 3H, J = 6.8 Hz), 1.16 (d, 3H, J = 6.8 Hz), 1.02 (t, 3H, J = 7.1 Hz).
143		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.85 (br s, 1H), 8.80 (s, 1H), 7.58-7.50 (m, 1H), 7.33-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.99-4.92 (m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 3.84 (dd, 1H, J = 13.8, 4.1 Hz), 3.79-3.68 (m, 2H), 3.65 (dd, 1H, J = 10.4, 7.9 Hz), 3.56-3.44 (m, 2H), 3.38-3.34 (m, 2H), 3.30-3.22 (m, 2H), 1.17 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz), 0.91 (t, 3H, J = 7.0 Hz).
144		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.82 (br s, 1H), 8.81 (s, 1H), 7.52-7.38 (m, 2H), 7.26-7.21 (m, 1H), 5.00-4.94 (m, 1H), 4.77 (sep, 1H, J = 6.9 Hz), 4.49 (s, 2H), 3.84 (dd, 1H, J = 13.7, 4.0 Hz), 3.75 (dd, 1H, J = 13.7, 1.2 Hz), 3.66-3.54 (m, 2H), 3.25 (s, 3H), 1.16 (d, 3H, J = 6.9 Hz), 1.16 (d, 3H, J = 6.9 Hz).

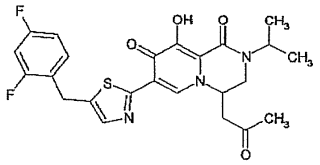
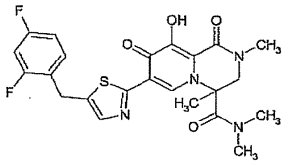
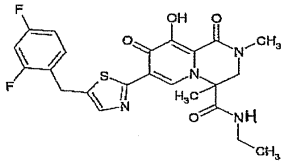
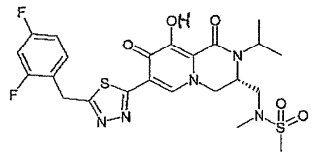
CUADRO 1-41

No.	Fórmula estructural	sal	^{1}H-NMR
145		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.45 (br s, 1H), 8.85 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.71–4.65 (m, 1H), 4.49 (s, 2H), 4.38–4.27 (m, 2H), 4.17–4.11 (m, 1H), 3.50 (dd, 1H, J = 10.5, 4.1 Hz), 3.39 (dd, 1H, J = 10.5, 7.7 Hz), 3.20 (s, 3H), 1.78–1.59 (m, 2H), 1.25 (d, 3H, J = 6.8 Hz), 0.86 (t, 3H, J = 7.4 Hz).
146		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.48 (br s, 1H), 8.83 (s, 1H), 7.57–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.65 (dd, 1H, J = 13.5, 1.1 Hz), 4.49 (s, 2H), 4.38 (dd, 1H, J = 13.5, 4.1 Hz), 4.15–4.03 (m, 2H), 3.50 (dd, 1H, J = 10.1, 4.2 Hz), 3.42 (dd, 1H, J = 10.1, 7.1 Hz), 3.20 (s, 3H), 1.83–1.73 (m, 1H), 1.63–1.53 (m, 1H), 1.33 (d, 3H, J = 6.8 Hz), 0.91 (t, 3H, J = 7.4 Hz).
147		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.85 (br s, 1H), 8.81 (s, 1H), 7.59–7.49 (m, 1H), 7.33–7.25 (m, 1H), 7.16–7.08 (m, 1H), 5.05–4.86 (br m, 1H), 4.60–4.50 (m, 1H), 4.49 (s, 2H), 3.87–3.56 (m, 4H), 3.25–3.25 (m, 3H), 1.54–1.50 (m, 2H), 1.15 (d, 3H, J = 6.5 Hz), 0.91–0.80 (m, 3H).

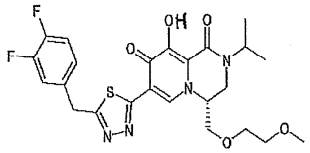
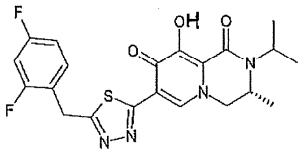
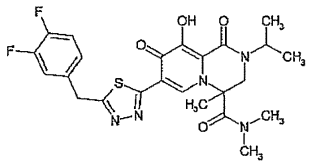
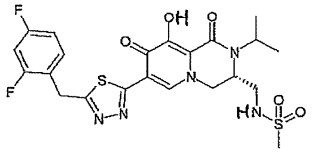
CUADRO 1-42

No.	Fórmula estructural	sal	^{1}H-NMR
148		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.87 (br s, 1H), 8.81 (s, 1H), 7.58–7.52 (m, 1H), 7.32–7.27 (m, 1H), 7.16–7.07 (m, 1H), 5.05–4.90 (m, 1H), 4.49 (s, 2H), 4.32–4.20 (m, 1H), 3.90–3.57 (m, 4H), 3.26–3.24 (m, 3H), 1.87–1.69 (m, 1H), 1.19–1.10 (m, 3H), 0.97–0.79 (m, 6H).
149		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.79 (br s, 1H), 8.90 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.97–4.88 (m, 1H), 4.84–4.74 (m, 1H), 4.49 (s, 2H), 3.81 (dd, 1H, J = 13.5, 3.7 Hz), 3.63 (dd, 1H, J = 13.5, 2.2 Hz), 1.39 (d, 3H, J = 6.6 Hz), 1.19 (d, 3H, J = 6.8 Hz), 1.16 (d, 3H, J = 6.8 Hz).
150		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.44 (br s, 1H), 8.85 (s, 1H), 7.53–7.37 (m, 2H), 7.26–7.19 (m, 1H), 4.66 (dd, 1H, J = 13.5, 1.5 Hz), 4.51–4.43 (m, 1H), 4.49 (s, 2H), 4.38–4.32 (m, 1H), 4.23–4.17 (m, 1H), 3.49 (dd, 1H, J = 10.4, 4.4 Hz), 3.39 (dd, 1H, J = 10.4, 7.5 Hz), 3.22 (s, 3H), 1.30 (d, 3H, J = 6.6 Hz), 1.29 (d, 3H, J = 6.8 Hz).

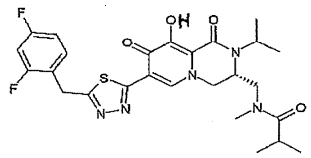
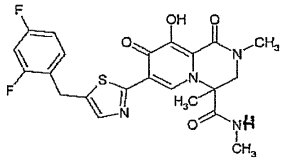
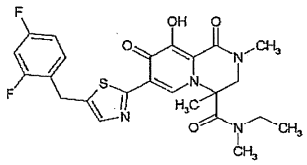
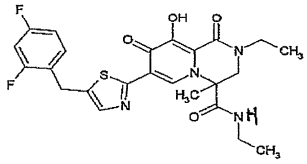
CUADRO 1-43

No.	Fórmula estructural	sal	^{1}H-NMR
151		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.86–12.34 (m, 1H), 8.68 (s, 1H), 7.66 (s, 1H), 7.49–7.39 (m, 1H), 7.29–7.20 (m, 1H), 7.11–7.02 (m, 1H), 5.12–5.03 (m, 1H), 4.84–4.70 (m, 1H), 4.21 (s, 2H), 3.82–3.55 (m, 2H), 3.15–2.96 (m, 2H), 2.08 (s, 3H), 1.17–1.09 (m, 6H).
152		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.77 (br s, 1H), 8.43 (s, 1H), 7.68 (s, 1H), 7.50–7.41 (m, 1H), 7.29–7.20 (m, 1H), 7.11–7.03 (m, 1H), 4.24–4.16 (m, 1H), 4.22 (s, 2H), 3.91 (d, 1H, J = 13.9 Hz), 3.07 (s, 3H), 2.89 (s, 6H), 1.92 (s, 3H).
153		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.64 (br s, 1H), 8.53 (s, 1H), 8.34–8.23 (m, 1H), 7.68 (s, 1H), 7.50–7.40 (m, 1H), 7.30–7.20 (m, 1H), 7.13–7.02 (m, 1H), 4.23 (s, 2H), 4.12 (d, 1H, J = 14.1 Hz), 4.01 (d, 1H, J = 14.1 Hz), 3.17–2.97 (m, 2H), 3.03 (s, 3H), 1.87 (s, 3H), 0.99 (t, 3H, J = 7.4 Hz).
154		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.32 (s, 1H), 8.79 (s, 1H), 7.58–7.50 (m, 1H), 7.32–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.60 (d, 1H, J = 13.0 Hz), 4.55 (sep, 1H, J = 6.8 Hz), 4.48 (s, 2H), 4.35 (dd, 1H, J = 13.0, 3.0 Hz), 4.27–4.20 (m, 1H), 3.26 (dd, 1H, J = 13.7, 10.5 Hz), 2.99 (dd, 1H, J = 13.7, 3.0 Hz), 2.87 (s, 3H), 2.84 (s, 3H), 1.30 (d, 6H, J = 6.8 Hz).

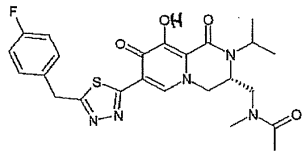
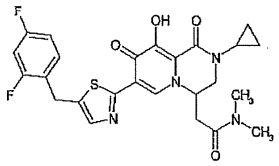
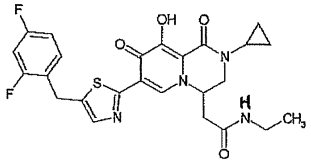
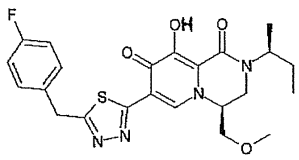
CUADRO 1-44

No.	Fórmula estructural	sal	^{1}H-NMR
155		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.83 (br s, 1H), 8.82 (s, 1H), 7.52-7.37 (m, 2H), 7.27-7.20 (m, 1H), 4.99-4.91 (m, 1H), 4.77 (sep, 1H, J = 6.9 Hz), 4.49 (s, 2H), 3.84 (dd, 1H, J = 13.7, 4.0 Hz), 3.79-3.69 (m, 2H), 3.64 (dd, 1H, J = 10.5, 7.7 Hz), 3.58-3.45 (m, 2H), 3.34 (t, 2H, J = 4.6 Hz), 3.11 (s, 3H), 1.17 (d, 3H, J = 6.9 Hz), 1.16 (d, 3H, J = 6.9 Hz).
156		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.84 (s, 1H), 7.58-7.50 (m, 1H), 7.33-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.62-4.53 (m, 1H), 4.51-4.45 (m, 3H), 4.32 (dd, 1H, J = 13.1, 3.4 Hz), 4.26-4.18 (m, 1H), 1.27 (d, 3H, J = 6.9 Hz), 1.26 (d, 3H, J = 6.9 Hz), 1.21 (d, 3H, J = 6.4 Hz).
157		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.96 (s, 1H), 8.56 (s, 1H), 7.53-7.19 (m, 3H), 4.80-4.66 (m, 1H), 4.50 (s, 2H), 4.15 (d, 1H, J = 14.3 Hz), 3.82 (d, 1H, J = 14.3 Hz), 3.09-2.83 (m, 6H), 2.04 (s, 3H), 1.18 (d, 3H, J = 7.1 Hz), 1.11 (d, 3H, J = 7.1 Hz).
158		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.35 (s, 1H), 8.75 (s, 1H), 7.57-7.49 (m, 2H), 7.32-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.61-4.53 (m, 2H), 4.49 (s, 2H), 4.40-4.33 (m, 1H), 4.00-3.93 (m, 1H), 3.21-3.12 (m, 1H), 3.02-2.92 (m, 1H), 2.90 (s, 3H), 1.30 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).

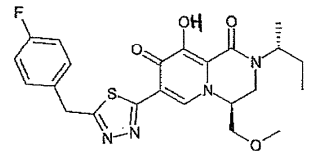
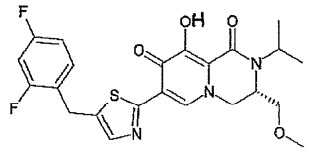
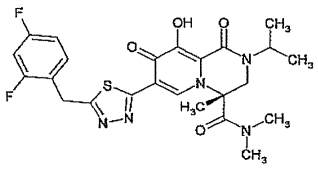
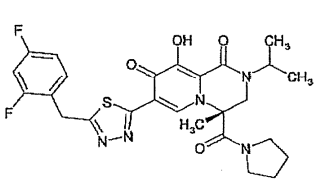
CUADRO 1-45

No.	Fórmula estructural	sal	^{1}H-NMR
159		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.39 (br s, 1H), 8.83 (s, 1H), 7.58–7.49 (m, 1H), 7.32–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.56 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.42–4.28 (m, 2H), 4.26–4.18 (m, 1H), 3.41–3.36 (m, 2H), 3.04 (s, 3H), 2.83 (t, 1H, J = 6.7 Hz), 1.34 (d, 3H, J = 6.7 Hz), 1.29 (d, 3H, J = 6.7 Hz), 1.00 (d, 3H, J = 6.7 Hz), 0.99 (d, 3H, J = 6.7 Hz).
160		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.67 (br s, 1H), 8.53 (s, 1H), 8.12–8.02 (m, 1H), 7.67 (s, 1H), 7.49–7.40 (m, 1H), 7.29–7.20 (m, 1H), 7.12–7.02 (m, 1H), 4.22 (s, 2H), 4.07 (d, 1H, J = 14.1 Hz), 3.99 (d, 1H, J = 14.1 Hz), 3.03 (s, 3H), 2.60 (d, 3H, J = 4.6 Hz), 1.86 (s, 3H).
161		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.76 (br s, 1H), 8.41 (s, 1H), 7.66 (s, 1H), 7.50–7.40 (m, 1H), 7.29–7.20 (m, 1H), 7.12–7.03 (m, 1H), 4.22 (s, 2H), 4.17 (d, 1H, J = 13.9 Hz), 3.91 (d, 1H, J = 13.9 Hz), 3.46–3.17 (m, 2H), 3.06 (s, 3H), 2.84 (s, 3H), 1.90 (s, 3H), 0.99 (t, 3H, J = 7.4 Hz).
162		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.71 (br s, 1H), 8.52 (s, 1H), 8.31–8.22 (m, 1H), 7.67 (s, 1H), 7.50–7.39 (m, 1H), 7.31–7.19 (m, 1H), 7.13–7.03 (m, 1H), 4.22 (s, 2H), 4.14 (d, 1H, J = 13.7 Hz), 3.99 (d, 1H, J = 13.7 Hz), 3.66–3.28 (m, 2H), 3.15–3.00 (m, 2H), 1.89 (s, 3H), 1.11 (t, 3H, J = 7.4 Hz), 0.99 (t, 3H, J = 7.4 Hz).

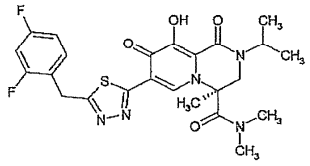
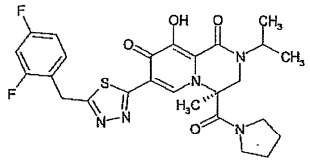
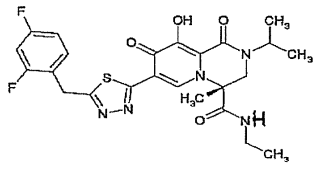
CUADRO 1-46

No.	Fórmula estructural	sal	^{1}H-NMR
163		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.34 (br s, 1H), 8.78 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.55 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 4.43 (d, 1H, J = 12.4 Hz), 4.38-4.27 (m, 1H), 4.25-4.17 (m, 1H), 3.44 (dd, 1H, J = 13.3, 10.0 Hz), 3.34-3.28 (m, 1H), 3.00 (s, 3H), 1.99 (s, 3H), 1.33 (d, 3H, J = 6.7 Hz), 1.29 (d, 3H, J = 6.7 Hz).
164		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.71 (s, 1H), 7.66 (s, 1H), 7.49-7.40 (m, 1H), 7.29-7.20 (m, 1H), 7.12-7.03 (m, 1H), 5.06-4.95 (m, 1H), 4.21 (s, 2H), 4.04 (dd, 1H, J = 13.4, 3.5 Hz), 3.68-3.60 (m, 1H), 2.97-2.88 (m, 1H), 2.88-2.82 (m, 2H), 2.87 (s, 3H), 2.79 (s, 3H), 0.96-0.83 (m, 2H), 0.83-0.72 (m, 1H), 0.67-0.55 (m, 1H).
165		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.52 (s, 1H), 7.99 (t, 1H, J = 4.9 Hz), 7.65 (s, 1H), 7.49-7.40 (m, 1H), 7.29-7.20 (m, 1H), 7.12-7.03 (m, 1H), 5.00-4.89 (m, 1H), 4.21 (s, 2H), 4.03 (dd, 1H, J = 13.9, 3.9 Hz), 3.58-3.50 (m, 1H), 3.03-2.83 (m, 3H), 2.56 (d, 2H, J = 7.4 Hz), 1.01-0.71 (m, 4H), 0.80 (t, 3H, J = 7.2 Hz).
166		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.81 (s, 1H), 7.47-7.36 (m, 2H), 7.23-7.12 (m, 2H), 5.04-4.91 (m, 1H), 4.60-4.49 (m, 1H), 4.47 (s, 2H), 3.88-3.54 (m, 4H), 3.27-3.23 (m, 3H), 1.61-1.46 (m, 2H), 1.15 (d, 3H, J = 6.4 Hz), 0.91-0.80 (m, 3H).

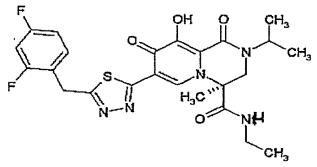
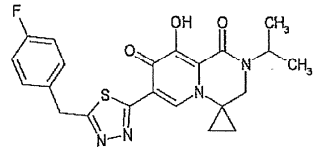
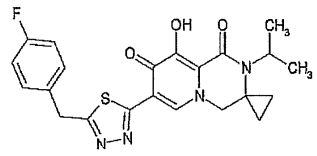
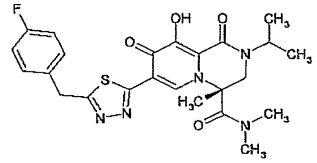
CUADRO 1-47

No.	Fórmula estructural	sal	^{1}H-NMR
167		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.81 (s, 1H), 7.46-7.38 (m, 2H), 7.23-7.14 (m, 2H), 5.02-4.92 (m, 1H), 4.60-4.49 (m, 1H), 4.47 (s, 2H), 3.89-3.54 (m, 4H), 3.27-3.23 (m, 3H), 1.59-1.47 (m, 2H), 1.15 (d, 3H, J = 6.4 Hz), 0.91-0.80 (m, 3H).
168		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.66 (s, 1H), 7.65 (s, 1H), 7.49-7.40 (m, 1H), 7.30-7.20 (m, 1H), 7.12-7.02 (m, 1H), 4.64-4.56 (m, 1H), 4.47 (sep, 1H, J = 6.7 Hz), 4.33 (dd, 1H, J = 13.3, 3.6 Hz), 4.24-4.14 (m, 3H), 3.48 (dd, 1H, J = 10.2, 4.2 Hz), 3.36 (dd, 1H, J = 10.2, 7.7 Hz), 3.21 (s, 3H), 1.29 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz).
169		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.96 (br s, 1H), 8.55 (s, 1H), 7.54 (td, 1H, J = 8.6, 6.6 Hz), 7.29 (ddd, 1H, J = 10.2, 9.3, 2.6 Hz), 7.11 (tdd, 1H, J = 8.6, 2.6, 0.9 Hz), 4.73 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.15 (d, 1H, J = 14.4 Hz), 3.82 (d, 1H, J = 14.4 Hz), 2.95 (br s, 6H), 2.03 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz).
170		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.91 (br s, 1H), 8.64 (s, 1H), 7.54 (td, 1H, J = 8.8, 6.6 Hz), 7.29 (ddd, 1H, J = 10.4, 9.5, 2.8 Hz), 7.12 (tdd, 1H, J = 8.8, 2.8, 1.2 Hz), 4.70 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.14 (d, 1H, J = 14.1 Hz), 3.77 (d, 1H, J = 14.1 Hz), 3.71-3.50 (br m, 2H), 3.36-3.24 (br m, 1H), 3.21-3.08 (br m, 1H), 2.06 (s, 3H), 1.97-1.86 (br m, 1H), 1.83-1.59 (br m, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.7 Hz).

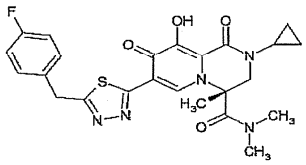
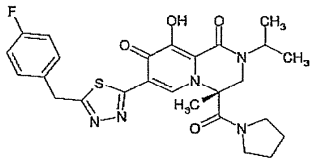
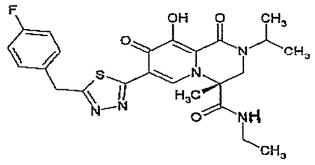
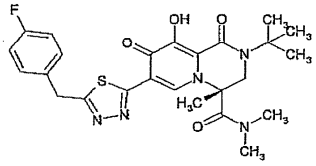
CUADRO 1-48

No.	Fórmula estructural	sal	^{1}H-NMR
171		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.96 (br s, 1H), 8.55 (s, 1H), 7.54 (td, 1H, J = 8.6, 6.6 Hz), 7.29 (ddd, 1H, J = 10.2, 9.3, 2.6 Hz), 7.11 (tdd, 1H, J = 8.6, 2.6, 0.9 Hz), 4.73 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.15 (d, 1H, J = 14.4 Hz), 3.82 (d, 1H, J = 14.4 Hz), 2.95 (br s, 6H), 2.03 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz).
172		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.91 (br s, 1H), 8.64 (s, 1H), 7.54 (td, 1H, J = 8.8, 6.6 Hz), 7.29 (ddd, 1H, J = 10.4, 9.5, 2.8 Hz), 7.12 (tdd, 1H, J = 8.8, 2.8, 1.2 Hz), 4.70 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.14 (d, 1H, J = 14.1 Hz), 3.77 (d, 1H, J = 14.1 Hz), 3.71–3.50 (br m, 2H), 3.36–3.24 (br m, 1H), 3.21–3.08 (br m, 1H), 2.06 (s, 3H), 1.97–1.86 (br m, 1H), 1.83–1.59 (br m, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.7 Hz).
173		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.93 (br s, 1H), 8.62 (s, 1H), 8.19 (t, 1H, J = 5.2 Hz), 7.54 (td, 1H, J = 8.7, 6.6 Hz), 7.29 (ddd, 1H, J = 10.4, 9.3, 2.6 Hz), 7.12 (tdd, 1H, J = 8.7, 2.6, 0.9 Hz), 4.71 (sep, 1H, J = 6.7 Hz), 4.50 (s, 2H), 4.11 (d, 1H, J = 13.9 Hz), 3.80 (d, 1H, J = 13.9 Hz), 3.18–2.98 (m, 2H), 1.96 (s, 3H), 1.15 (d, 3H, J = 6.7 Hz), 1.12 (d, 3H, J = 6.7 Hz), 1.00 (t, 3H, J = 7.2 Hz).

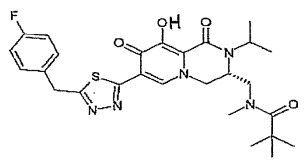
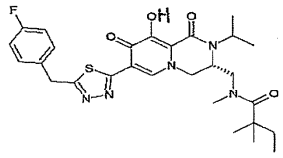
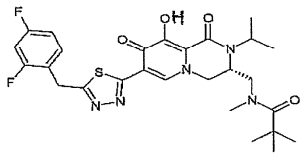
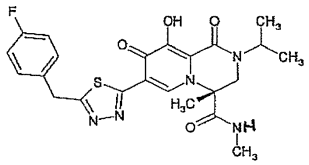
CUADRO 1-49

No.	Fórmula estructural	sal	^{1}H-NMR
174		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.93 (br s, 1H), 8.62 (s, 1H), 8.19 (t, 1H, J = 5.2 Hz), 7.54 (td, 1H, J = 8.7, 6.6 Hz), 7.29 (ddd, 1H, J = 10.4, 9.3, 2.6 Hz), 7.12 (tdd, 1H, J = 8.7, 2.6, 0.9 Hz), 4.71 (sep, 1H, J = 6.7 Hz), 4.50 (s, 2H), 4.11 (d, 1H, J = 13.9 Hz), 3.80 (d, 1H, J = 13.9 Hz), 3.18-2.98 (m, 2H), 1.96 (s, 3H), 1.15 (d, 3H, J = 6.7 Hz), 1.12 (d, 3H, J = 6.7 Hz), 1.00 (t, 3H, J = 7.2 Hz).
175		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.43 (s, 1H), 7.42-7.37 (m, 2H), 7.21-7.15 (m, 2H), 4.76 (sep, 1H, J = 6.9 Hz), 4.46 (s, 2H), 3.66 (s, 2H), 1.66-1.61 (m, 2H), 1.13-1.18 (m, 2H), 1.16 (d, 6H, J = 6.9 Hz).
176		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.67 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.47 (s, 2H), 4.31 (s, 2H), 4.15 (sep, 1H, J = 6.9 Hz), 1.35-1.29 (m, 2H), 1.32 (d, 6H, J = 6.9 Hz), 1.07-1.02 (m, 2H).
177		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.95 (s, 1H), 8.55 (s, 1H), 7.44-7.36 (m, 2H), 7.21-7.15 (m, 2H), 4.73 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.15 (d, 1H, J = 14.1 Hz), 3.82 (d, 1H, J = 14.1 Hz), 3.07-2.81 (br m, 6H), 2.04 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz).

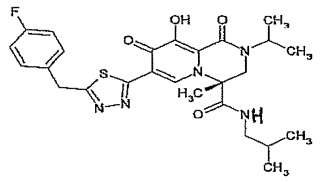
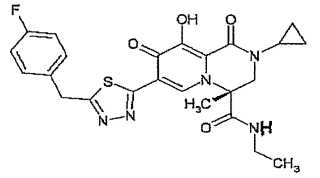
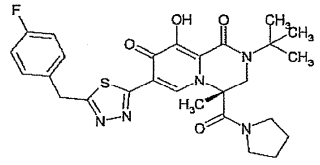
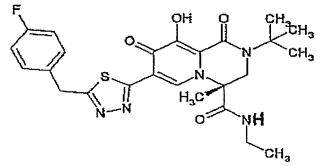
CUADRO 1-50

No.	Fórmula estructural	sal	^{1}H-NMR
178		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.87 (s, 1H), 8.55 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.14 (m, 2H), 4.48 (s, 2H), 4.15 (d, 1H, J = 13.9 Hz), 3.85 (d, 1H, J = 13.9 Hz), 2.95-2.83 (m, 1H), 2.89 (s, 6H), 1.97 (s, 3H), 0.95-0.80 (m, 2H), 0.76-0.62 (m, 2H).
179		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.90 (s, 1H), 8.65 (s, 1H), 7.45-7.38 (m, 2H), 7.23-7.15 (m, 2H), 4.70 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.14 (d, 1H, J = 13.9 Hz), 3.77 (d, 1H, J = 13.9 Hz), 3.72-3.62 (br m, 1H), 3.36-3.23 (br m, 2H), 3.20-3.09 (br m, 1H), 2.06 (s, 3H), 1.98-1.84 (br m, 1H), 1.83-1.59 (br m, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.7 Hz).
180		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.92 (s, 1H), 8.62 (s, 1H), 8.17 (t, 1H, J = 5.2 Hz), 7.44-7.37 (m, 2H), 7.23-7.15 (m, 2H), 4.71 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.10 (d, 1H, J = 13.9 Hz), 3.80 (d, 1H, J = 13.9 Hz), 3.18-2.99 (m, 2H), 1.96 (s, 3H), 1.15 (d, 3H, J = 6.7 Hz), 1.12 (d, 3H, J = 6.7 Hz), 1.01 (t, 3H, J = 7.2 Hz).
181		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.98 (br s, 1H), 8.59 (s, 1H), 7.45-7.37 (m, 2H), 7.23-7.15 (m, 2H), 4.47 (s, 2H), 4.32 (d, 1H, J = 14.4 Hz), 3.82 (d, 1H, J = 14.4 Hz), 2.90 (s, 6H), 2.03 (s, 3H), 1.45 (s, 9H).

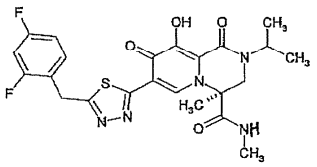
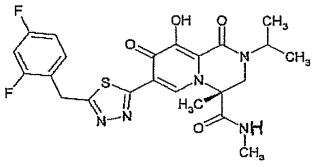
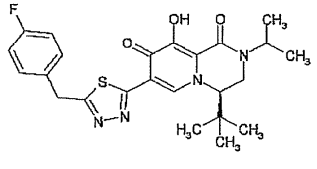
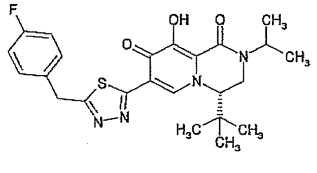
CUADRO 1-51

No.	Fórmula estructural	sal	^{1}H-NMR
182		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.91 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.55 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 4.43-4.29 (m, 2H), 4.26-4.19 (m, 1H), 3.47 (dd, 1H, J = 13.3, 4.0 Hz), 3.28 (dd, 1H, J = 13.3, 10.0 Hz), 3.12 (s, 3H), 1.35 (d, 3H, J = 6.7 Hz), 1.30 (d, 3H, J = 6.7 Hz), 1.20 (s, 9H).
183		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.92 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.55 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 4.38-4.33 (m, 2H), 4.22-4.16 (m, 1H), 3.47 (dd, 1H, J = 13.5, 3.5 Hz), 3.28 (dd, 1H, J = 13.5, 10.0 Hz), 3.12 (s, 3H), 1.65-1.57 (m, 2H), 1.35 (d, 3H, J = 6.7 Hz), 1.30 (d, 3H, J = 6.7 Hz), 1.17 (s, 3H), 1.16 (s, 3H), 0.79 (t, 3H, J = 7.5 Hz).
184		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.41 (br s, 1H), 8.90 (s, 1H), 7.58-7.50 (m, 1H), 7.32-7.25 (m, 1H), 7.15-7.08 (m, 1H), 4.56 (sep, 1H, J = 6.6 Hz), 4.49 (s, 2H), 4.41-4.29 (m, 2H), 4.27-4.18 (m, 1H), 3.48-3.44 (m, 1H), 3.29 (dd, 1H, J = 13.5, 10.0 Hz), 3.12 (s, 3H), 1.35 (d, 3H, J = 6.7 Hz), 1.30 (d, 3H, J = 6.7 Hz), 1.20 (s, 9H).
185		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.90 (br s, 1H), 8.63 (s, 1H), 8.12 (q, 1H, J = 4.4 Hz), 7.45-7.37 (m, 2H), 7.23-7.15 (m, 2H), 4.70 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.08 (d, 1H, J = 13.9 Hz), 3.80 (d, 1H, J = 13.9 Hz), 2.59 (d, 3H, J = 4.4 Hz), 1.97 (s, 3H), 1.15 (d, 3H, J = 6.7 Hz), 1.09 (d, 3H, J = 6.7 Hz).

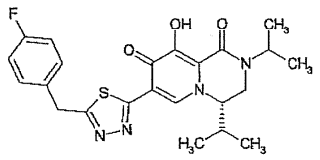
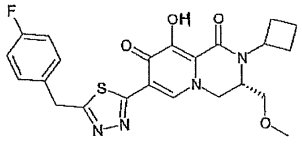
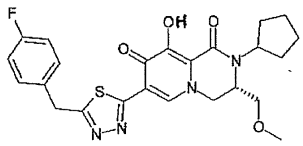
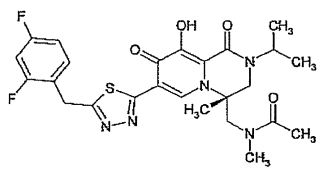
CUADRO 1-52

No.	Fórmula estructural	sal	^{1}H-NMR
186		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.93 (br s, 1H), 8.64 (s, 1H), 8.09 (t, 1H, J = 6.0 Hz), 7.43–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.69 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.14 (d, 1H, J = 13.9 Hz), 3.79 (d, 1H, J = 13.9 Hz), 3.10–3.01 (m, 1H), 2.71–2.62 (m, 1H), 1.97 (s, 3H), 1.75–1.61 (m, 1H), 1.15 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz), 0.79 (d, 6H, J = 6.7 Hz).
187		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.85 (br s, 1H), 8.62 (s, 1H), 8.19 (t, 1H, J = 5.2 Hz), 7.45–7.36 (m, 2H), 7.22–7.15 (m, 2H), 4.48 (s, 2H), 4.00 (d, 1H, J = 13.7 Hz), 3.96 (d, 1H, J = 13.7 Hz), 3.11–3.02 (m, 2H), 2.88 (sep, 1H, J = 3.9 Hz), 1.92 (s, 3H), 0.98 (t, 3H, J = 7.0 Hz), 0.96–0.89 (m, 1H), 0.85–0.69 (m, 2H), 0.65–0.56 (m, 1H).
188		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.93 (br s, 1H), 8.69 (s, 1H), 7.45–7.39 (m, 2H), 7.22–7.15 (m, 2H), 4.48 (s, 2H), 4.32 (d, 1H, J = 13.9 Hz), 3.77 (d, 1H, J = 13.9 Hz), 3.44–3.23 (br m, 4H), 2.01 (s, 3H), 1.92–1.54 (br m, 4H), 1.44 (s, 9H).
189		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.98 (br s, 1H), 8.59 (s, 1H), 8.19 (t, 1H, J = 7.0 Hz), 7.44–7.37 (m, 2H), 7.23–7.15 (m, 2H), 4.48 (s, 2H), 4.23 (d, 1H, J = 13.7 Hz), 3.83 (d, 1H, J = 13.7 Hz), 3.10 (dq, 2H, J = 7.0, 7.0 Hz), 1.94 (s, 3H), 1.45 (s, 9H), 1.02 (t, 3H, J = 7.0 Hz).

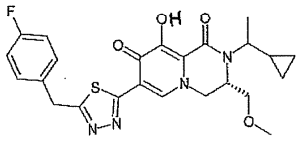
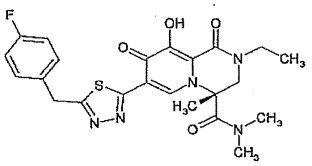
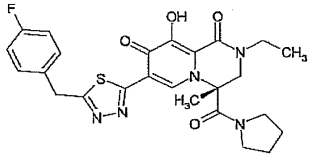
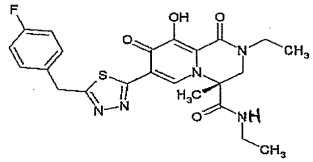
CUADRO 1-53

No.	Fórmula estructural	sal	^{1}H-NMR
190		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.90 (br s, 1H), 8.62 (s, 1H), 8.10 (q, 1H, J = 4.4 Hz), 7.53 (td, 1H, J = 8.6, 6.5 Hz), 7.28 (ddd, 1H, J = 10.2, 9.5, 2.6 Hz), 7.11 (tdd, 1H, J = 8.6, 2.6, 1.1 Hz), 4.69 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.06 (d, 1H, J = 13.9 Hz), 3.78 (d, 1H, J = 13.9 Hz), 2.58 (d, 3H, J = 4.4 Hz), 1.95 (s, 3H), 1.13 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.7 Hz).
191		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.90 (br s, 1H), 8.62 (s, 1H), 8.10 (q, 1H, J = 4.4 Hz), 7.53 (td, 1H, J = 8.6, 6.5 Hz), 7.28 (ddd, 1H, J = 10.2, 9.5, 2.6 Hz), 7.11 (tdd, 1H, J = 8.6, 2.6, 1.1 Hz), 4.69 (sep, 1H, J = 6.7 Hz), 4.49 (s, 2H), 4.06 (d, 1H, J = 13.9 Hz), 3.78 (d, 1H, J = 13.9 Hz), 2.58 (d, 3H, J = 4.4 Hz), 1.95 (s, 3H), 1.13 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.7 Hz).
192		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.88 (br s, 1H), 8.82 (s, 1H), 7.45-7.39 (m, 2H), 7.22-7.16 (m, 2H), 4.77 (sep, 1H, J = 6.9 Hz), 4.63-4.59 (m, 1H), 4.47 (s, 2H), 3.89-3.82 (m, 2H), 1.27 (d, 3H, J = 6.9 Hz), 1.19 (d, 3H, J = 6.9 Hz), 0.96 (s, 9H).
193		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.88 (br s, 1H), 8.82 (s, 1H), 7.45-7.39 (m, 2H), 7.22-7.16 (m, 2H), 4.77 (sep, 1H, J = 6.9 Hz), 4.63-4.59 (m, 1H), 4.47 (s, 2H), 3.89-3.83 (m, 2H), 1.28 (d, 3H, J = 6.9 Hz), 1.19 (d, 3H, J = 6.9 Hz), 0.96 (s, 9H).

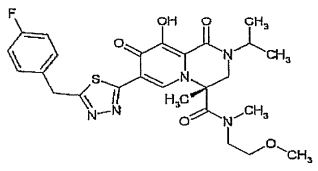
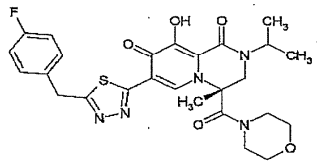
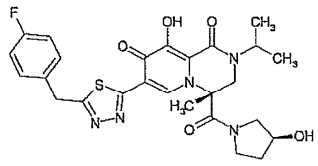
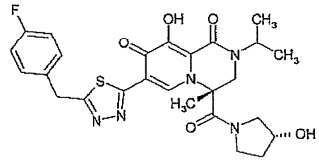
CUADRO 1-54

No.	Fórmula estructural	sal	^{1}H-NMR
194		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.76 (br s, 1H), 8.90 (s, 1H), 7.45–7.39 (m, 2H), 7.22–7.16 (m, 2H), 4.79–4.79 (sep, 1H, J = 6.7 Hz), 4.50–4.43 (m, 1H), 4.47 (s, 2H), 3.86–3.78 (m, 2H), 2.03–1.92 (m, 1H), 1.20 (d, 3H, J = 6.7 Hz), 1.18 (d, 3H, J = 6.7 Hz), 1.04 (d, 3H, J = 6.7 Hz), 0.69 (d, 3H, J = 6.7 Hz).
195		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.49 (br s, 1H), 8.85 (s, 1H), 7.44–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.68 (dd, 1H, J = 13.5, 1.3 Hz), 4.61–4.49 (m, 1H), 4.47 (s, 2H), 4.41 (dd, 1H, J = 13.5, 4.0 Hz), 4.31–4.25 (m, 1H), 3.43 (dd, 1H, J = 10.6, 5.0 Hz), 3.39 (dd, 1H, J = 10.6, 6.8 Hz), 3.21 (s, 3H), 2.38–2.11 (m, 4H), 1.77–1.64 (m, 2H).
196		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.49 (br s, 1H), 8.85 (s, 1H), 7.44–7.37 (m, 2H), 7.22–7.15 (m, 2H), 4.65 (dd, 1H, J = 13.7, 1.5 Hz), 4.47 (s, 2H), 4.44–4.34 (m, 2H), 4.20–4.13 (m, 1H), 3.47 (dd, 1H, J = 10.4, 4.6 Hz), 3.41 (dd, 1H, J = 10.4, 7.3 Hz), 3.21 (s, 3H), 1.95–1.72 (m, 6H), 1.63–1.49 (m, 2H).
197		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.29 (br s, 1H), 8.52 (s, 1H), 7.60–7.50 (m, 1H), 7.36–7.25 (m, 1H), 7.17–7.08 (m, 1H), 4.86–4.73 (m, 1H), 4.49 (s, 2H), 3.91–3.64 (m, 4H), 2.82 (s, 3H), 1.81 (s, 3H), 1.71 (s, 3H), 1.23 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 7.0 Hz).

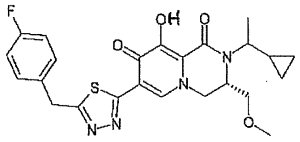
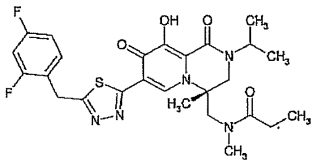
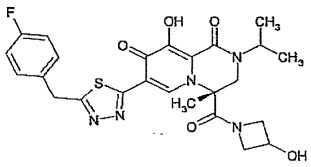
CUADRO 1-55

No.	Fórmula estructural	sal	^{1}H-NMR
198		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.88 (s, 1H), 7.45–7.37 (m, 2H), 7.23–7.15 (m, 2H), 4.70 (d, 1H, J = 13.0 Hz), 4.47 (s, 2H), 4.39–4.27 (m, 2H), 3.73–3.61 (m, 2H), 3.49–3.41 (m, 1H), 3.22 (s, 3H), 1.34 (d, 3H, J = 6.7 Hz), 1.26–1.13 (m, 1H), 0.69–0.60 (m, 1H), 0.54–0.45 (m, 1H), 0.42–0.27 (m, 2H).
199		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.87 (s, 1H), 8.56 (s, 1H), 7.45–7.37 (m, 2H), 7.23–7.15 (m, 2H), 4.48 (s, 2H), 4.21 (d, 1H, J = 13.9 Hz), 3.98 (d, 1H, J = 13.9 Hz), 3.53 (q, 2H, J = 7.0 Hz), 2.50 (s, 6H), 2.01 (s, 3H), 1.11 (t, 3H, J = 7.0 Hz).
200		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.81 (br s, 1H), 8.67 (s, 1H), 7.45–7.39 (m, 2H), 7.22–7.15 (m, 2H), 4.48 (s, 2H), 4.19 (d, 1H, J = 13.9 Hz), 3.96 (d, 1H, J = 13.9 Hz), 3.59–3.25 (br m, 3H), 3.53 (dq, 1H, J = 14.0, 7.0 Hz), 3.49 (dq, 1H, J = 14.0, 7.0 Hz), 3.12–2.96 (br m, 1H), 2.01 (s, 3H), 1.96–1.48 (m, 4H), 1.09 (t, 3H, J = 7.0 Hz).
201		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.81 (br s, 1H), 8.62 (s, 1H), 8.26 (t, 1H, J = 5.6 Hz), 7.44–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.48 (s, 2H), 4.13 (d, 1H, J = 13.9 Hz), 4.01 (d, 1H, J = 13.9 Hz), 3.62 (dq, 1H, J = 14.2, 7.1 Hz), 3.36 (dq, 1H, J = 14.2, 7.1 Hz), 3.14–3.04 (m, 2H), 1.93 (s, 3H), 1.11 (t, 3H, J = 7.1 Hz), 1.00 (t, 3H, J = 7.1 Hz).

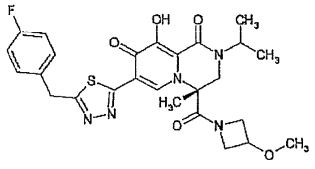
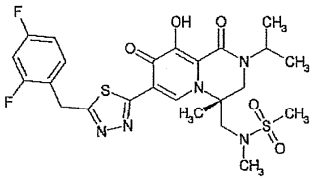
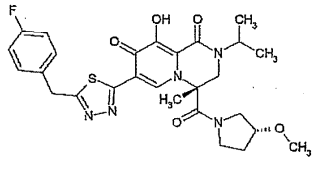
CUADRO 1-56

No.	Fórmula estructural	sal	^{1}H-NMR
202		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.00 (br s, 1H), 8.57 (s, 1H), 7.45-7.37 (m, 2H), 7.22-7.15 (m, 2H), 4.72 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.18 (d, 1H, J = 14.4 Hz), 3.81 (d, 1H, J = 14.4 Hz), 3.64 (br s, 3H), 3.42 (t, 2H, J = 5.3 Hz), 3.20 (s, 3H), 3.05-2.92 (br m, 2H), 2.02 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.13 (d, 3H, J = 6.7 Hz).
203		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.06 (br s, 1H), 8.52 (s, 1H), 7.46-7.38 (m, 2H), 7.23-7.15 (m, 2H), 4.75 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.05 (d, 1H, J = 14.4 Hz), 3.84 (d, 1H, J = 14.4 Hz), 3.62-3.48 (br m, 8H), 1.98 (s, 3H), 1.18 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
204		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.95 (br s, 1H), 8.68-8.61 (m, 1H), 7.45-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.69 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.23-4.15 (br m, 1H), 4.11 (d, 1H, J = 13.9 Hz), 3.76 (d, 1H, J = 13.9 Hz), 3.69-3.59 (br m, 1H), 3.46-3.36 (br m, 2H), 3.30-2.88 (br m, 1H), 2.09-2.00 (m, 3H), 2.02-1.55 (br m, 2H), 1.21-1.06 (m, 6H).
205		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.91 (br s, 1H), 8.71-8.61 (m, 1H), 7.46-7.37 (m, 2H), 7.24-7.14 (m, 2H), 4.69 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.33-4.13 (br m, 2H), 4.08 (d, 1H, J = 13.9 Hz), 3.77 (d, 1H, J = 13.9 Hz), 3.51-3.15 (br m, 3H), 2.14-2.01 (m, 3H), 1.89-1.61 (br m, 2H), 1.21-1.02 (m, 6H).

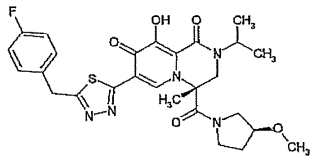
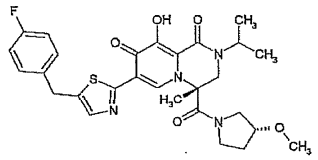
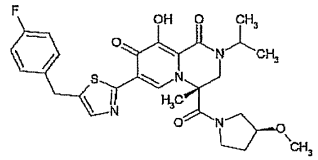
CUADRO 1-57

No.	Fórmula estructural	sal	^{1}H-NMR
206		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.87 (s, 1H), 7.44–7.38 (m, 2H), 7.23–7.15 (m, 2H), 4.72 (d, 1H, J = 12.3 Hz), 4.47 (s, 2H), 4.43–4.33 (m, 2H), 3.67–3.58 (m, 1H), 3.57–3.51 (m, 1H), 3.47–3.40 (m, 1H), 3.22 (s, 3H), 1.34 (d, 3H, J = 6.7 Hz), 1.31–1.21 (m, 1H), 0.68–0.59 (m, 1H), 0.54–0.46 (m, 1H), 0.44–0.36 (m, 1H), 0.32–0.24 (m, 1H).
207		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.31 (br s, 1H), 8.48 (s, 1H), 7.59–7.49 (m, 1H), 7.38–7.22 (m, 1H), 7.20–7.05 (m, 1H), 4.87–4.73 (m, 1H), 4.48 (s, 2H), 4.02–3.86 (m, 1H), 3.80 (d, 1H, J = 13.7 Hz), 3.71 (d, 1H, J = 13.7 Hz), 3.47–3.32 (m, 1H), 2.85 (s, 3H), 2.17–2.04 (m, 2H), 1.71 (s, 3H), 1.23 (d, 3H, J = 7.0 Hz), 1.17 (d, 3H, J = 7.0 Hz), 0.65 (t, 3H, J = 7.4 Hz).
208		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.93 (br s, 1H), 8.72 (s, 1H), 7.45–7.38 (m, 2H), 7.23–7.15 (m, 2H), 4.69 (sep, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.44–4.27 (br m, 2H), 4.11–3.82 (br m, 2H), 4.02 (d, 1H, J = 13.9 Hz), 3.72 (d, 1H, J = 13.9 Hz), 3.64–3.40 (br m, 1H), 1.99 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.12 (d, 3H, J = 6.7 Hz).

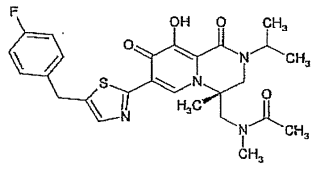
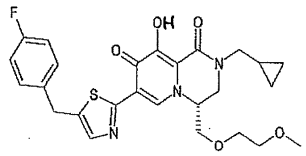
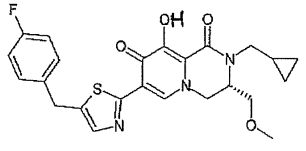
CUADRO 1-58

No.	Fórmula estructural	sal	^{1}H-NMR
209		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.89 (br s, 1H), 8.71 (s, 1H), 7.45–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.70 (sep, 1H, J = 6.8 Hz), 4.48 (s, 2H), 4.22–3.90 (br m, 4H), 4.00 (d, 1H, J = 13.9 Hz), 3.74–3.57 (br m, 1H), 3.74 (d, 1H, J = 13.9 Hz), 3.14 (s, 3H), 2.00 (s, 3H), 1.19–1.09 (m, 6H).
210		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.30 (s, 1H), 8.60 (s, 1H), 7.56–7.50 (m, 1H), 7.35–7.25 (m, 1H), 7.13–7.08 (m, 1H), 4.80–4.74 (m, 1H), 4.47 (s, 2H), 3.75 (s, 2H), 3.48–3.30 (m, 2H), 2.84 (s, 3H), 2.57 (s, 3H), 1.74 (s, 3H), 1.24 (d, 3H, J=6.7 Hz), 1.15 (d, 3H, J=6.7 Hz).
211		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.91 (s, 0.5H), 12.86 (s, 0.5H), 8.68 (s, 0.5H), 8.60 (s, 0.5H), 7.42–7.38 (m, 2H), 7.20–7.15 (m, 2H), 4.72–4.65 (m, 1H), 4.47 (s, 2H), 4.16 (d, 0.5H, J = 13.7Hz), 4.08 (d, 0.5H, J = 13.7 Hz), 4.00–3.98 (m, 0.5H), 3.86–3.84 (m, 0.5H) 3.81–3.74 (m, 2H), 3.51–3.33 (m, 3H), 3.17 (s, 3H), 2.54–2.49 (m, 2H), 2.07 (s, 3H), 1.15 (d, 3H, J=6.7 Hz), 1.05 (d, 3H, J=6.7 Hz).

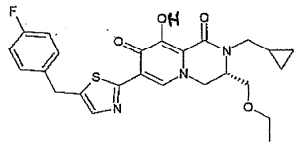
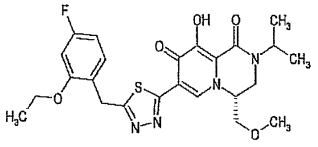
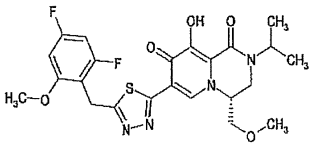
CUADRO 1-59

No.	Fórmula estructural	sal	^{1}H-NMR
212		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.94 (s, 1H), 8.66 (s, 0.5H), 8.62 (s, 0.5H), 7.42-7.38 (m, 2H), 7.20-7.15 (m, 2H), 4.70-4.65 (m, 1H), 4.47 (s, 2H), 4.11-4.06 (m, 1H), 3.93-3.90 (m, 1H), 3.87-3.84 (m, 1H), 3.81-3.75 (m, 1H) 3.69-3.65 (m, 1H), 3.62-3.45 (m, 1H), 3.17 (s, 1.5H), 3.15 (s, 1.5H), 3.10-3.06 (m, 1H), 2.07 (s, 1.5H), 2.05 (s, 1.5H), 1.99-1.96 (m, 1H), 1.79-1.76 (m, 1H), 1.16 (d, 3H, J=6.7 Hz), 1.06 (d, 3H, J=6.7 Hz).
213		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.77 (br s, 1H), 8.55 (s, 0.5H), 8.48 (s, 0.5H), 7.67 (s, 1H), 7.34-7.29 (m, 2H), 7.17-7.11 (m, 2H), 4.71-4.65 (m, 1H), 4.25-4.04 (m, 1H), 4.20 (s, 2H), 3.98-3.86 (m, 0.5H), 3.85-3.84 (m, 0.5H), 3.78-3.68 (m, 2H), 3.50-3.25 (m, 2H), 3.17 (s, 1.5H), 3.15 (s, 1.5H), 2.54-2.49 (m, 1H), 2.02 (s, 3H), 1.91-1.85 (m, 1H), 1.78-1.71 (m, 1H), 1.15 (d, 3H, J = 6.7 Hz), 1.05 (d, 3H, J=6.7 Hz).
214		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.84 (br s, 1H), 8.54 (s, 0.5H), 8.50 (s, 0.5H), 7.68 (s, 1H), 7.34-7.31 (m, 2H), 7.17-7.11 (m, 2H), 4.71-4.65 (m, 1H), 4.20 (s, 2H), 4.07 (dd, 1H, J=13.9, 5.3 Hz), 3.90-3.85 (m, 1H), 3.75 (dd, 1H, J=13.9, 7.4 Hz), 3.59-3.36 (m, 3H), 3.15 (s, 3H), 2.54-2.49 (m, 1H), 2.02 (s, 1.5H), 1.99 (s, 1.5H), 1.99-1.97 (m, 1H), 1.78-1.71 (m, 1H), 1.16 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J=6.7 Hz).

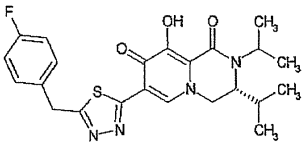
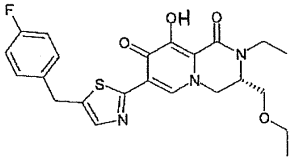
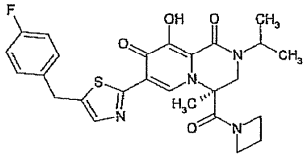
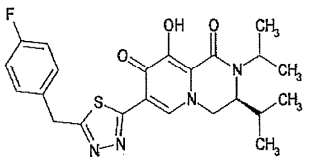
CUADRO 1-60

No.	Fórmula estructural	sal	^{1}H-NMR
215		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.20 (br s, 1H), 8.44 (s, 1H), 7.67 (s, 1H), 7.35-7.31 (m, 2H), 7.16-7.11 (m, 2H), 4.81-4.74 (m, 1H), 4.19 (s, 2H), 3.79-3.65 (m, 3H), 3.57 (d, 1H, J=14.4 Hz), 2.74 (s, 3H), 1.81 (s, 3H), 1.66 (s, 3H), 1.21 (d, 3H, J=6.7 Hz), 1.15 (d, 3H, J=6.7 Hz).
216		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.60 (br s, 1H), 8.63 (s, 1H), 7.66 (s, 1H), 7.35-7.30 (m, 2H), 7.17-7.11 (m, 2H), 4.89-4.85 (m, 1H), 4.19 (s, 2H), 4.08 (dd, 1H, J=13.7, 4.2 Hz), 3.81 (d, 1H, J=13.7 Hz), 3.57 (dd, 1H, J=10.5, 5.7 Hz), 3.66 (dd, 1H, J=10.5, 7.9 Hz), 3.56-3.39 (m, 3H), 3.33-3.27 (m, 3H), 3.10 (s, 3H), 1.10-1.04 (m, 1H), 0.55-0.46 (m, 2H), 0.36-0.26 (m, 2H).
217		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.30 (br s, 1H), 8.65 (s, 1H), 7.66 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.60 (d, 1H, J=13.2 Hz), 4.42 (dd, 1H, J=13.2, 3.9 Hz), 4.24-4.19 (m, 1H), 4.19 (s, 2H), 3.67 (dd, 1H, J=14.2, 7.0 Hz), 3.55 (dd, 1H, J=10.3, 4.8 Hz), 3.47 (dd, 1H, J=10.3, 7.0 Hz), 3.20 (s, 3H), 3.19 (dd, 1H, J=14.2, 7.4 Hz), 1.18-1.12 (m, 1H), 0.55-0.46 (m, 2H), 0.41-0.37 (m, 1H), 0.31-0.28 (m, 1H).

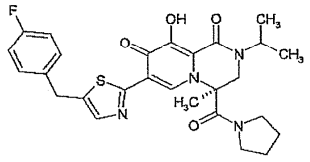
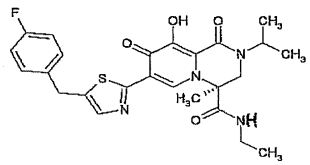
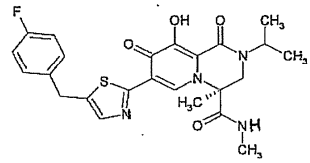
CUADRO 1-61

No.	Fórmula estructural	sal	^{1}H-NMR
218		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.30 (br s, 1H), 8.65 (s, 1H), 7.66 (s, 1H), 7.34-7.31 (m, 2H), 7.16-7.11 (m, 2H), 4.61 (d, 1H, J=13.5 Hz), 4.42 (dd, 1H, J=13.5, 4.2 Hz), 4.24-4.19 (m, 1H), 4.19 (s, 2H), 3.67 (dd, 1H, J=14.0, 7.1 Hz), 3.60 (dd, 1H, J=10.3, 4.2 Hz), 3.52 (dd, 1H, J=10.3, 6.4 Hz), 3.42-3.30 (m, 2H), 3.20 (dd, 1H, J=14.0, 7.0 Hz), 1.16-1.11 (m, 1H), 0.95 (t, 3H, J=7.0 Hz), 0.56-0.46 (m, 2H), 0.41-0.37 (m, 1H), 0.31-0.27 (m, 1H).
219		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.79 (br s, 1H), 8.78 (s, 1H), 7.35 (dd, 1H, J = 8.4, 7.0 Hz), 6.93 (dd, 1H, J = 11.4, 2.6 Hz), 6.74 (td, 1H, J = 8.4, 2.6 Hz), 4.97-4.93 (m, 1H), 4.79-4.72, (m, 1H), 4.33 (s, 2H), 4.06 (q, 2H, J=7.0 Hz), 3.79-3.65 (m, 2H), 3.61 (dd, 1H, J=10.3, 5.7 Hz), 3.55 (dd, 1H, J=10.3, 7.7 Hz), 3.23 (s, 3H), 1.31 (t, 3H, J=7.0 Hz), 1.15 (d, 3H, J=2.3 Hz), 1.14 (d, 3H, J=2.3 Hz).
220		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.80 (s, 1H), 8.76 (s, 1H), 6.93-6.87 (m, 2H), 4.97-4.93 (m, 1H), 4.79-4.72 (m, 1H), 4.33 (s, 2H), 3.85 (s, 3H), 3.84-3.72 (m, 2H), 3.61 (dd, 1H, J=10.3, 5.7 Hz), 3.55 (dd, 1H, J=10.3, 7.8 Hz), 3.23 (s, 3H), 1.15 (d, 3H, J=2.3 Hz), 1.14 (d, 3H, J=2.3 Hz).

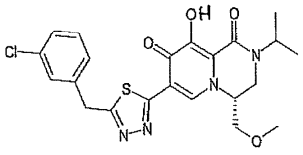
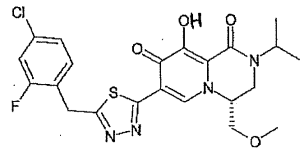
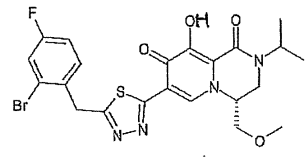
CUADRO 1-62

No.	Fórmula estructural	sal	^{1}H-NMR
221		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.50 (br s, 1H), 9.02 (s, 1H), 7.43–7.39 (m, 2H), 7.21–7.16 (m, 2H), 4.76 (d, 1H, J=13.3 Hz), 4.47 (s, 2H), 4.30 (dd, 1H, J=13.3, 4.6 Hz), 4.21–4.14 (m, 1H), 3.83 (br t, 1H, J=4.6 Hz), 2.04–1.99 (m, 1H), 1.39 (d, 3H, J=6.9 Hz), 1.35 (d, 3H, J=6.9 Hz), 1.05 (d, 3H, J=6.9Hz), 0.64 (d, 3H, J=6.9 Hz).
222		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.30 (br s, 1H), 8.65 (s, 1H), 7.67 (s, 1H), 7.35–7.31 (m, 2H), 7.18–7.13 (m, 2H), 4.59, (br d, 1H, J=13.3 Hz), 4.41 (dd, 1H, J=13.3, 4.1 Hz), 4.20 (s, 2H), 4.12–4.09 (m, 1H), 3.89–3.84 (m, 1H), 3.58–3.50 (m, 2H), 3.41–3.34 (m, 2H), 3.29–3.24 (m, 1H), 1.20 (t, 3H, J=7.2 Hz), 0.97 (t, 3H, J=7.0Hz).
223		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (m, 1H), 8.59 (s, 1H), 7.69 (s, 1H), 7.34–7.30 (m, 2H), 7.17–7.11 (m, 2H), 4.72–4.65 (m, 1H), 4.20 (s, 2H), 4.20–4.13 (m, 1H), 4.00 (d, 1H, J=13.5 Hz), 3.86–3.80 (m, 2H), 3.75–3.66 (m, 2H), 2.12–2.03 (m, 2H), 1.93 (s, 3H), 1.14 (d, 3H, J=6.7 Hz), 1.12 (d, 3H, J=6.7 Hz).
224		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.55 (br s, 1H), 9.02 (s, 1H), 7.43–7.39 (m, 2H), 7.21–7.16 (m, 2H), 4.76 (d, 1H, J=13.3 Hz), 4.47 (s, 2H), 4.30 (dd, 1H, J=13.3, 4.6 Hz), 4.21–4.14 (m, 1H), 3.83 (br t, 1H, J=4.6 Hz), 2.04–1.99 (m, 1H), 1.39 (d, 3H, J = 6.9 Hz), 1.35 (d, 3H, J=6.9 Hz), 1.05 (d, 3H, J=6.9 Hz), 0.64 (d, 3H, J=6.9 Hz).

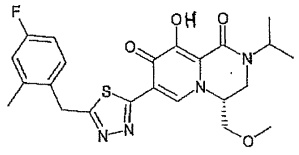
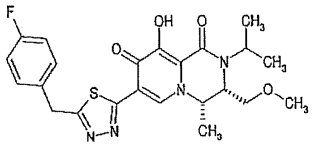
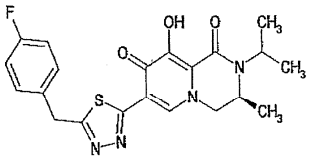
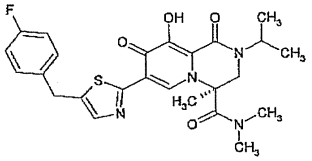
CUADRO 1-63

No.	Fórmula estructural	sal	^{1}H-NMR
225		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.78 (s, 1H), 8.52 (s, 1H), 7.67 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.12 (m, 2H), 4.72-4.66 (m, 1H), 4.19 (s, 2H), 4.11 (d, 1H, J=13.9 Hz), 3.74 (d, 1H, J=13.9 Hz), 3.41-3.25 (m, 1H), 3.13-3.06 (m, 1H), 3.81-3.74 (m, 2H), 2.00 (s, 3H), 1.92-1.84 (m, 1H), 1.75-1.61 (m, 3H), 1.15 (d, 3H, J=6.7 Hz), 1.07 (d, 3H, J=6.7 Hz).
226		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.81 (br s, 1H), 8.51 (s, 1H), 8.20 (br t, 1H, J=5.5 Hz), 7.67 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.73-4.66 (m, 1H), 4.20 (s, 2H), 4.11 (d, 1H, J=13.7 Hz), 3.77 (d, 1H, J=13.7 Hz), 3.13-2.99 (m, 2H), 1.92 (s, 3H), 1.14 (d, 3H, J=6.7 Hz), 1.10 (d, 3H, J=6.7 Hz), 0.99 (t, 3H, J=7.2 Hz).
227		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.80 (br s, 1H), 8.54 (s, 1H), 8.22 (d, 1H, J=4.4 Hz), 7.69 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.12 (m, 2H), 4.73-4.66 (m, 1H), 4.20 (s, 2H), 4.13 (d, 1H, J=13.7 Hz), 3.78 (d, 1H, J=13.7 Hz), 2.57 (d, 3H, J=4.4 Hz), 1.93 (s, 3H), 1.13 (d, 3H, J=7.0 Hz), 1.08 (d, 3H, J=7.0 Hz).

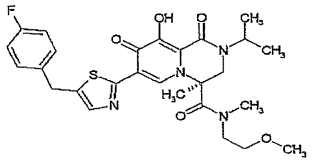
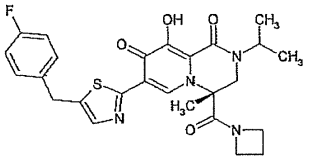
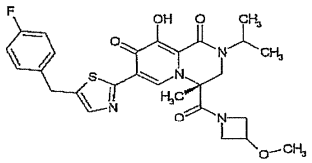
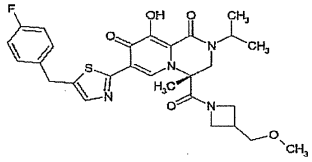
CUADRO 1-64

No.	Fórmula estructural	sal	^{1}H-NMR
228		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.85 (br s, 1H), 8.81 (s, 1H), 7.48-7.46 (m, 1H), 7.42-7.33 (m, 3H), 4.98-4.96 (m, 1H), 4.80-4.73 (m, 1H), 4.50 (s, 2H), 3.84 (dd, 1H, J=13.8, 4.1 Hz), 3.75 (br d, 1H, J=13.8 Hz), 3.63 (dd, 1H, J=10.4, 5.7 Hz), 3.57 (dd, 1H, J=10.4, 7.5 Hz), 3.25 (s, 3H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz).
229		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.83 (br s, 1H), 8.80 (s, 1H), 7.51 (t, 1H, J=8.3 Hz), 7.48 (dd, 1H, J=8.3, 2.0 Hz), 7.32 (dd, 1H, J=8.3, 2.0 Hz), 5.00-4.95 (m, 1H), 4.80-4.74 (m, 1H), 4.50 (s, 2H), 3.84 (dd, 1H, J=13.7, 4.0 Hz), 3.75 (dd, 1H, J=13.7, 1.6 Hz), 3.62 (dd, 1H, J=10.3, 5.8 Hz), 3.57 (dd, 1H, J=10.3, 7.7 Hz), 3.25 (s, 3H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz).
230		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.83 (br s, 1H), 8.79 (s, 1H), 7.66 (dd, 1H, J=8.7, 2.6 Hz), 7.61 (dd, 1H, J=8.7, 6.0 Hz), 7.32 (td, 1H, J=8.7, 2.6 Hz), 4.99-4.95 (m, 1H), 4.80-4.74 (m, 1H), 4.57 (s, 2H), 3.84 (dd, 1H, J=13.7, 4.0 Hz), 3.75 (dd, 1H, J=13.7, 1.6 Hz), 3.62 (dd, 1H, J=10.3, 5.8 Hz), 3.57 (dd, 1H, J=10.3, 7.7 Hz), 3.25 (s, 3H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz).

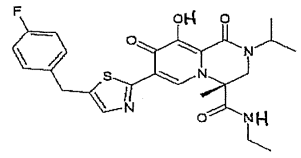
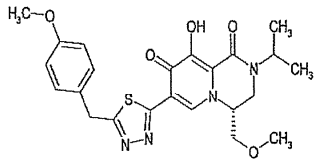
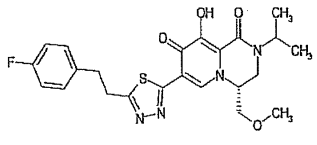
CUADRO 1-65

No.	Fórmula estructural	sal	^{1}H-NMR
231		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.80 (br s, 1H), 8.79 (s, 1H), 7.37 (dd, 1H, J=8.5, 6.1 Hz), 7.10-7.01 (m, 2H), 4.99-4.95 (m, 1H), 4.80-4.74 (m, 1H), 4.45 (s, 2H), 3.84 (dd, 1H, J=13.7, 4.1 Hz), 3.75 (br d, 1H, J=13.7 Hz), 3.62 (dd, 1H, J=10.4, 5.7 Hz), 3.57 (dd, 1H, J=10.4, 7.6 Hz), 3.25 (s, 3H), 2.29 (s, 3H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz).
232		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (br s, 1H), 8.56 (s, 1H), 7.42-7.38 (m, 2H), 7.20-7.16 (m, 2H), 4.66-4.64 (m, 1H), 4.47 (s, 2H), 4.45-4.40 (m, 1H), 4.08-4.05 (m, 1H), 3.56 (dd, 1H, J=11.3, 3.2 Hz), 3.50 (dd, 1H, J=11.3, 4.2 Hz), 3.11 (s, 3H), 1.75 (d, 3H, J=6.5 Hz), 1.33 (d, 3H, J=6.0 Hz), 1.32 (d, 3H, J=6.0 Hz).
233		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.54 (br s, 1H), 8.85 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.62-4.53 (m, 1H), 4.51-4.44 (m, 3H), 4.32 (dd, 1H, J = 13.1, 3.4 Hz), 4.26-4.18 (m, 1H), 1.27 (d, 3H, J = 6.7 Hz), 1.26 (d, 3H, J = 6.7 Hz), 1.21 (d, 3H, J = 6.5 Hz).
234		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.85 (s, 1H), 8.43 (s, 1H), 7.69 (s, 1H), 7.37-7.29 (m, 2H), 7.19-7.11 (m, 2H), 4.73 (sep, 1H, J = 6.7 Hz), 4.21 (s, 2H), 4.12 (d, 1H, J = 14.1 Hz), 3.79 (d, 1H, J = 14.1 Hz), 2.93 (s, 6H), 1.98 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 6.7 Hz).

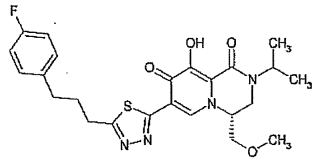
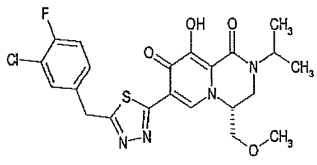
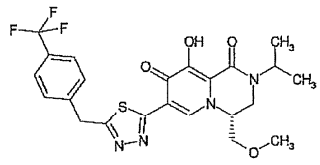
CUADRO 1-66

No.	Fórmula estructural	sal	^{1}H-NMR
235		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.89 (br s, 1H), 8.46 (s, 1H), 7.69 (s, 1H), 7.34-7.31 (m, 2H), 7.16-7.12 (m, 2H), 4.74-4.68 (m, 1H), 4.20 (s, 2H), 4.15 (d, 1H, J = 14.2 Hz), 3.78 (d, 1H, J = 14.2 Hz), 3.60-3.53 (m, 1H), 3.40 (br t, 2H, J = 5.2 Hz), 3.36-3.28 (m, 1H), 3.18 (s, 3H), 2.95 (br s, 3H), 1.97 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.12 (d, 3H, J = 6.7 Hz).
236		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.80 (m, 1H), 8.59 (s, 1H), 7.69 (s, 1H), 7.34-7.30 (m, 2H), 7.17-7.11 (m, 2H), 4.72-4.65 (m, 1H), 4.20 (s, 2H), 4.20-4.13 (m, 1H), 4.00 (d, 1H, J=13.5 Hz), 3.86-3.80 (m, 2H), 3.75-3.66 (m, 2H), 2.12-2.03 (m, 2H), 1.93 (s, 3H), 1.14 (d, 3H, J=6.7 Hz), 1.12 (d, 3H, J=6.7 Hz).
237		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.77 (br s, 1H), 8.55 (s, 1H), 7.69 (s, 1H), 7.34-7.30 (m, 2H), 7.17-7.11 (m, 2H), 4.72-4.66 (m, 1H), 4.20 (s, 2H), 4.17-3.96 (m, 4H), 3.73-3.53 (m, 3H), 3.12 (s, 3H), 2.95 (s, 3H), 1.18-1.07 (m, 6H).
238		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.80 (br s, 1H), 8.58-8.53 (m, 1H), 7.69-7.68 (m, 1H), 7.34-7.30 (m, 2H), 7.16-7.12 (m, 2H), 4.72-4.66 (m, 2H), 4.20 (s, 2H), 3.99-3.84 (m, 2H), 3.78-3.67 (m, 1H), 3.60-3.47 (m, 2H), 3.36-3.33 (m, 2H), 3.27-3.25 (m, 1H), 3.28-3.16 (m, 3H), 1.93 (s, 3H), 1.15-1.10 (m, 6H).

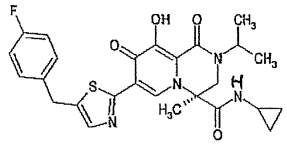
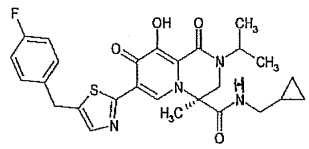
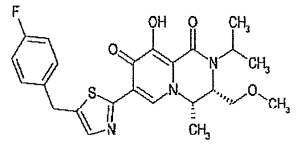
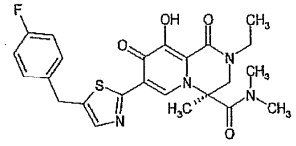
CUADRO 1-67

No.	Fórmula estructural	sal	^{1}H-NMR
239		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.81 (br s, 1H), 8.51 (s, 1H), 8.20 (br t, 1H, J=5.5 Hz), 7.67 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.73-4.66 (m, 1H), 4.20 (s, 2H), 4.11 (d, 1H, J=13.7 Hz), 3.77 (d, 1H, J=13.7 Hz), 3.13-2.99 (m, 2H), 1.92 (s, 3H), 1.14 (d, 3H, J=6.7 Hz), 1.10 (d, 3H, J=6.7 Hz), 0.99 (t, 3H, J=7.2 Hz).
240		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.80 (br s, 1H), 8.80 (s, 1H), 7.29 (d, 2H, J=8.9 Hz), 6.92 (d, 2H, J=8.9 Hz), 4.99-4.94 (m, 1H), 4.80-4.73 (m, 1H), 4.39 (s, 2H), 3.84 (dd, 1H, J=13.7, 4.0 Hz), 3.75 (d, 1H, J=13.7 Hz), 3.74 (s, 3H), 3.62 (dd, 1H, J=10.3, 5.8 Hz), 3.57 (dd, 1H, J=10.3, 7.7 Hz), 3.25 (s, 3H), 1.17 (d, 3H, J=2.4 Hz), 1.15 (d, 3H, J=2.4 Hz).
241		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.80 (br s, 1H), 8.80 (s, 1H), 7.32 (dd, 2H, J=8.5, 5.6 Hz), 7.11 (t, 2H, J=8.5 Hz), 4.98-4.94 (m, 1H), 4.81-4.74 (m, 1H), 3.84 (dd, 1H, J=13.9, 3.8 Hz), 3.76 (d, 1H, J=13.9 Hz), 3.63 (dd, 1H, J=10.3, 5.8 Hz), 3.57 (dd, 1H, J=10.3, 7.5 Hz), 3.41 (t, 2H, J=7.7 Hz), 3.26 (s, 3H), 3.09 (t, 2H, J=7.7 Hz), 1.17 (d, 3H, J=1.6 Hz), 1.15 (d, 3H, J=1.6 Hz).

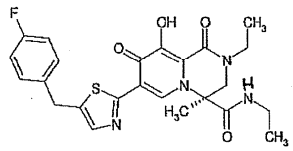
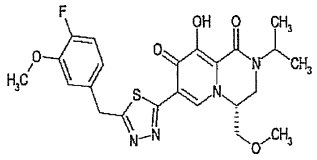
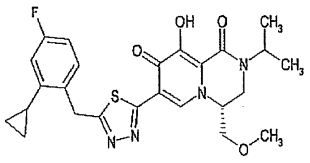
CUADRO 1-68

No.	Fórmula estructural	sal	^{1}H-NMR
242		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.81 (br s, 1H), 8.81 (s, 1H), 7.28 (dd, 2H, J=8.5, 5.6 Hz), 7.11 (t, 2H, J=8.5 Hz), 4.98-4.94 (m, 1H), 4.81-4.74 (m, 1H), 3.85 (dd, 1H, J=13.9, 4.0 Hz), 3.76 (dd, 1H, J=13.9, 1.4 Hz), 3.63 (dd, 1H, J=10.3, 5.8 Hz), 3.58 (dd, 1H, J=10.3, 7.7 Hz), 3.26 (s, 3H), 3.10 (t, 2H, J=7.7 Hz), 2.68 (t, 2H, J=7.7 Hz), 2.09-2.01 (m, 2H), 1.18 (d, 3H, J=2.0 Hz), 1.16 (d, 3H, J=2.0 Hz).
243		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.81 (s, 1H), 7.65-7.63 (m, 1H), 7.41-7.39 (m, 2H), 5.00-4.95 (m, 1H), 4.80-4.74 (m, 1H), 4.50 (s, 2H), 3.84 (dd, 1H, J=13.7, 4.0 Hz), 3.76 (dd, 1H, J=13.7, 1.6 Hz), 3.63 (dd, 1H, J=10.1, 5.6 Hz), 3.57 (dd, 1H, J=10.1, 7.7 Hz), 3.25 (s, 3H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz).
244		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.81 (s, 1H), 7.73 (d, 2H, J=8.1 Hz), 7.60 (d, 2H, J=8.1 Hz), 4.99-4.94 (m, 1H), 4.80-4.73 (m, 1H), 4.61 (s, 2H), 3.84 (dd, 1H, J=13.7, 4.0 Hz), 3.76 (dd, 1H, J=13.7, 1.6 Hz), 3.63 (dd, 1H, J=10.1, 5.6 Hz), 3.57 (dd, 1H, J=10.1, 7.7 Hz), 3.25 (s, 3H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz).

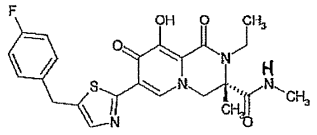
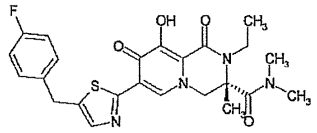
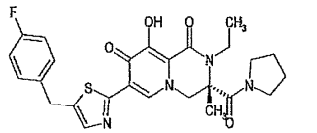
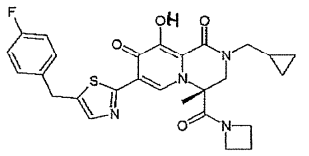
CUADRO 1-69

No.	Fórmula estructural	sal	^{1}H-NMR
245		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.79 (br s, 1H), 8.48 (s, 1H), 8.34-8.33 (m, 1H), 7.67 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.12 (m, 2H), 4.73-4.67 (m, 1H), 4.20 (s, 2H), 4.06 (d, 1H, J=13.7 Hz), 3.78 (d, 1H, J=13.7 Hz), 3.61-3.44 (m, 1H), 1.90 (s, 3H), 1.13 (d, 3H, J=6.7 Hz), 1.09 (d, 3H, J=6.7 Hz), 0.62 (d, 2H, J=7.4 Hz), 0.46-0.41 (m, 2H).
246		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.82 (br s, 1H), 8.51 (s, 1H), 8.28 (t, 1H, J=5.5 Hz), 7.67 (s, 1H), 7.33-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.73-4.66 (m, 1H), 4.20 (s, 2H), 4.15 (d, 1H, J=13.9 Hz), 3.78 (d, 1H, J=13.9 Hz), 2.98-2.84 (m, 2H), 1.93 (s, 3H), 1.14 (d, 3H, J=7.2 Hz), 1.12 (d, 3H, J=7.2 Hz), 0.89-0.85 (m, 1H), 0.40-0.37 (m, 2H), 0.14-0.10 (m, 2H).
247		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.70 (br s, 1H), 8.51 (s, 1H), 7.71 (s, 1H), 7.34-7.30 (m, 2H), 7.18-7.12 (m, 2H), 4.64-4.62 (m, 1H), 4.45-4.49 (m, 1H), 4.21 (s, 2H), 4.06-4.02 (m, 1H), 3.53 (dd, 1H, J=11.1, 3.4 Hz), 3.48 (dd, 1H, J=11.1, 4.2 Hz), 3.11 (s, 3H), 1.72 (d, 3H, J=6.5 Hz), 1.33 (d, 3H, J=5.6 Hz), 1.31 (d, 3H, J=5.6 Hz).
248		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (br s, 1H), 8.44 (s, 1H), 7.68 (s, 1H), 7.37-7.29 (m, 2H), 7.16-7.11 (m, 2H), 4.20 (s, 2H), 4.19 (d, 1H, J = 14.1 Hz), 3.93 (d, 1H, J = 14.1 Hz), 3.56-3.44 (m, 2H), 2.90 (s, 6H), 1.94 (s, 3H), 1.10 (s, 3H, J=7.2 Hz).

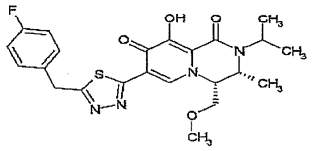
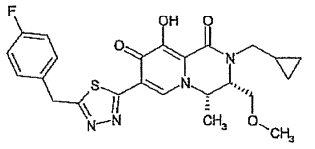
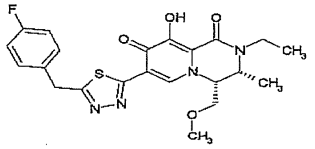
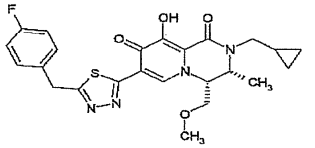
CUADRO 1-70

No.	Fórmula estructural	sal	^{1}H-NMR
249		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.68 (br s, 1H), 8.50 (s, 1H), 8.20 (br t, 1H, J=5.1 Hz), 7.67 (s, 1H), 7.33-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.20 (s, 2H), 4.09 (d, 1H, J = 13.7 Hz), 3.97 (d, 1H, J = 13.7 Hz), 3.64-3.55 (m, 1H), 3.38-3.32 (m, 1H), 3.11-3.04 (m, 2H), 1.88 (s, 3H), 1.10 (s, 3H, J=7.2 Hz), 0.98 (s, 3H, J=7.2 Hz).
250		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.79 (br s, 1H), 8.81 (s, 1H), 7.23-7.16 (m, 2H), 6.94-6.90 (m, 1H), 4.99-4.95 (m, 1H), 4.80-4.74 (m, 1H), 4.45 (s, 2H), 3.86-3.83 (m, 1H), 3.83 (s, 3H), 3.76 (dd, 1H, J=13.9, 1.4 Hz), 3.63 (dd, 1H, J=10.3, 5.8 Hz), 3.57 (dd, 1H, J=10.3, 7.7 Hz), 3.25 (s, 3H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz).
251		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (br s, 1H), 8.79 (s, 1H), 7.38 (dd, 1H, J=8.5, 6.5 Hz), 7.02 (td, 1H, 8.5, 2.8 Hz), 6.81 (dd, 1H, J=8.5, 2.8 Hz), 4.98-4.94 (m, 1H), 4.78-4.64 (m, 1H), 4.60 (s, 2H), 3.83 (dd, 1H, J=13.7, 4.0 Hz), 3.75 (dd, 1H, J=13.7, 1.4 Hz), 3.62 (dd, 1H, J=10.3, 5.8 Hz), 3.57 (dd, 1H, J=10.3, 7.7 Hz), 3.25 (s, 3H), 2.06-1.99 (m, 1H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz), 0.90-0.84 (m, 2H), 0.66-0.63 (m, 2H).

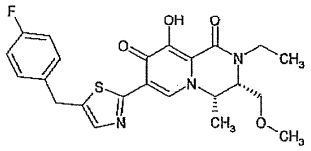
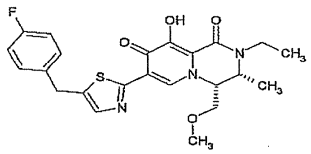
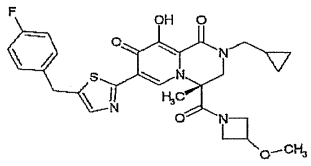
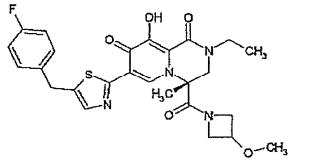
CUADRO 1-71

No.	Fórmula estructural	sal	^{1}H-NMR
252		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.40 (br s, 1H), 8.52 (s, 1H), 8.09-8.05 (m, 1H), 7.65 (s, 1H), 7.34-7.29 (m, 2H), 7.16-7.10 (m, 2H), 4.67 (d, 1H, J=13.5 Hz), 4.37 (d, 1H, J=13.5 Hz), 4.19 (s, 2H), 3.76-3.68 (m, 1H), 3.38-3.29 (m, 1H), 2.54 (d, 3H, J=4.4 Hz), 1.65 (s, 3H), 1.51 (t, 3H, J=7.1 Hz).
253		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.40 (br s, 1H), 8.68 (s, 1H), 7.66 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.86 (d, 1H, J=14.1 Hz), 4.46 (d, 1H, J=14.1 Hz), 4.19 (s, 2H), 3.78-3.69 (m, 1H), 3.18-3.09 (m, 1H), 2.99 (br s, 6H), 1.71 (s, 3H), 1.19 (t, 3H, J=7.1 Hz).
254		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.42 (br s, 1H), 8.69 (s, 1H), 7.65 (s, 1H), 7.34-7.29 (m, 2H), 7.16-7.11 (m, 2H), 4.86 (d, 1H, J=13.9 Hz), 4.46 (d, 1H, J=13.9 Hz), 4.30-4.03 (m, 1H), 4.19 (s, 2H), 3.78-3.68 (m, 2H), 3.46-3.17 (m, 3H), 1.98-1.78 (m, 4H), 1.73 (s, 3H), 1.17 (t, 3H, J=7.1 Hz).
255		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.70 (br s, 1H), 8.61 (s, 1H), 7.70 (s, 1H), 7.35-7.32 (m, 2H), 7.17-7.13 (m, 2H), 4.21 (s, 2H), 4.21-4.17 (m, 1H), 4.11 (d, 1H, J=13.7 Hz), 3.96 (d, 1H, J=13.7 Hz), 3.89-3.82 (m, 2H), 3.78-3.73 (m, 1H), 3.46 (dd, 1H, J=13.9, 6.9 Hz), 3.25 (dd, 1H, J=13.9, 7.5 Hz), 2.14-2.06 (m, 2H), 1.94 (s, 3H), 1.09-1.03 (m, 1H), 0.52-0.49 (m, 2H), 0.34-0.31 (m, 2H).

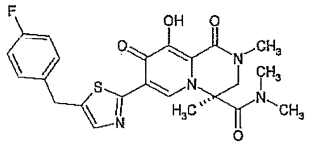
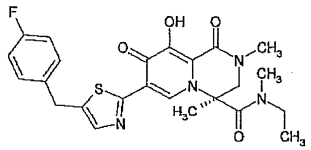
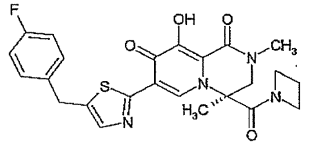
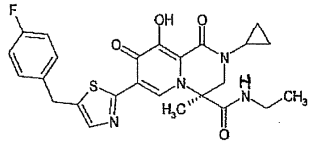
CUADRO 1-72

No.	Fórmula estructural	sal	^{1}H-NMR
256		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.77 (br s, 1H), 8.78 (s, 1H), 7.42-7.39 (m, 2H), 7.20-7.16 (m, 2H), 4.72-4.70 (m, 1H), 4.60-4.53 (m, 1H), 4.47 (s, 2H), 4.18-4.10 (m, 2H), 3.94 (dd, 1H, J=11.9, 2.2 Hz), 3.46 (s, 3H), 1.29 (d, 3H, J=6.9 Hz), 1.27 (d, 3H, J=6.9 Hz), 1.05 (d, 3H, J=6.5 Hz).
257		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.76 (br s, 1H), 8.62 (s, 1H), 7.42-7.38 (m, 2H), 7.20-7.16 (m, 2H), 4.77-4.74 (m, 1H), 4.47 (s, 2H), 4.19 (q, 1H, J=4.0 Hz), 3.71 (dd, 1H, J=14.1, 7.3 Hz), 3.62 (d, 2H, J=4.4 Hz), 3.23 (dd, 1H, J=14.1, 6.9 Hz), 3.16 (s, 3H), 1.69 (d, 3H, J=6.9 Hz), 1.22-1.16 (m, 1H), 0.58-0.48 (m, 2H), 0.44-0.39 (m, 1H), 0.34-0.29 (m, 1H).
258		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.82 (br s, 1H), 8.72 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.84-4.79 (m, 1H), 4.47 (s, 2H), 4.26-4.21 (m, 1H), 3.89-3.76 (m, 3H), 3.33 (s, 3H), 3.33-3.26 (m, 1H), 1.24 (d, 3H, J=6.9 Hz), 1.17 (t, 3H, J=7.3 Hz).
259		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.78 (br s, 1H), 8.74 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.85-4.81 (m, 1H), 4.47 (s, 2H), 4.30-4.24 (m, 1H), 3.93 (dd, 1H, J=11.5, 8.5 Hz), 3.85 (dd, 1H, J=11.5, 3.0 Hz), 3.56 (dd, 1H, J=14.1, 7.5 Hz), 3.37 (s, 3H), 3.30 (dd, 1H, J=14.1, 6.9 Hz), 1.24 (d, 3H, J=6.9 Hz), 1.15-1.09 (m, 1H), 0.58-0.48 (m, 2H), 0.41-0.30 (m, 2H).

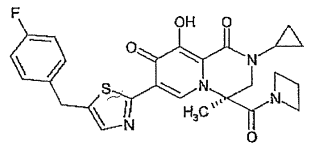
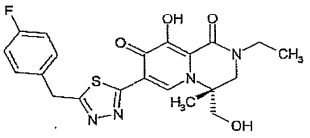
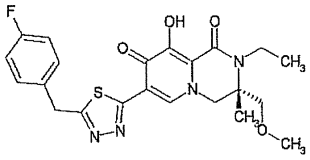
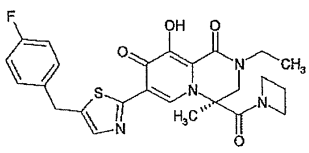
CUADRO 1-73

No.	Fórmula estructural	sal	^{1}H-NMR
260		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.67 (br s, 1H), 8.53 (s, 1H), 7.69 (s, 1H), 7.33-7.29 (m, 2H), 7.17-7.11 (m, 2H), 4.73-4.67 (m, 1H), 4.19 (s, 2H), 4.10 (q, 1H, J=4.1 Hz), 3.90-3.83 (m, 1H), 3.56 (d, 2H, J=4.6 Hz), 3.33-3.32 (m, 1H), 3.16 (s, 3H), 1.61 (d, 3H, J=6.5 Hz), 1.20 (t, 3H, J=7.1 Hz).
261		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.69 (br s, 1H), 8.59 (s, 1H), 7.67 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.79-4.75 (m, 1H), 4.22-4.19 (m, 1H), 4.19 (s, 2H), 3.85-3.73 (m, 3H), 3.31 (s, 3H), 3.31-3.24 (m, 1H), 1.22 (d, 3H, J=6.7 Hz), 1.15 (t, 3H, J=7.1 Hz).
262		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.71 (br s, 1H), 8.60 (s, 1H), 7.70 (s, 1H), 7.35-7.31 (m, 2H), 7.16-7.12 (m, 2H), 4.41-4.38 (m, 1H), 4.20 (s, 2H), 4.10-4.02 (m, 4H), 3.98 (d, 1H, J=13.7 Hz), 3.68-3.59 (m, 1H), 3.43-3.35 (m, 1H), 3.32-3.26 (m, 1H), 3.13 (s, 3H), 1.94 (s, 3H), 1.07-1.00 (m, 1H), 0.53-0.45 (m, 2H), 0.34-0.28 (m, 2H).
263		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.69 (br s, 1H), 8.60 (s, 1H), 7.69 (s, 1H), 7.34-7.31 (m, 2H), 7.14 (br t, 2H, J=8.8 Hz), 4.39-4.36 (m, 1H), 4.20 (s, 2H), 4.11-3.90 (m, 5H), 3.69-3.65 (m, 1H), 3.57-3.40 (m, 2H), 3.12 (s, 3H), 1.92 (s, 3H), 1.09 (t, 3H, J=6.6 Hz).

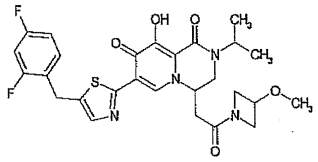
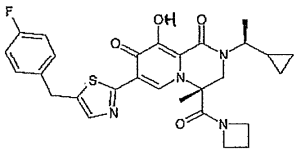
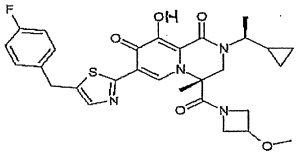
CUADRO 1-74

No.	Fórmula estructural	sal	^{1}H-NMR
264		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (s, 1H), 8.41 (s, 1H), 7.68 (s, 1H), 7.32 (dd, 2H, J=8.2, 5.9 Hz), 7.16-7.13 (m, 2H), 4.19 (s, 2H), 4.18 (d, 1H, J = 13.9 Hz), 3.90 (d, 1H, J = 13.9 Hz), 3.05 (s, 3H), 2.88 (s, 6H), 1.91 (s, 3H).
265		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (s, 1H), 8.40 (s, 1H), 7.67 (s, 1H), 7.35-7.29 (m, 2H), 7.16-7.11 (m, 2H), 4.19 (s, 2H), 4.17 (d, 1H, J = 13.9 Hz), 3.89 (d, 1H, J = 13.9 Hz), 3.43-3.35 (m, 1H), 3.28-3.19 (m, 1H), 3.05 (s, 3H), 2.83 (s, 3H), 1.89 (s, 3H), 0.98 (t, 3H, J=7.1 Hz).
266		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.66 (br s, 1H), 8.62 (s, 1H), 7.70 (s, 1H), 7.34-7.31 (m, 2H), 7.16-7.12 (m, 2H), 4.20 (s, 2H), 4.18-4.11 (m, 1H), 4.04-3.97 (m, 1H), 3.91-3.82 (m, 2H), 3.28-3.19 (m, 1H), 3.64-3.57 (m, 1H), 3.03 (s, 3H), 2.09-2.03 (m, 2H), 1.90 (s, 3H).
267		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.73 (br s, 1H), 8.50 (s, 1H), 8.18 (br t, 1H, J=5.6 Hz), 7.67 (s, 1H), 7.34-7.29 (m, 2H), 7.17-7.11 (m, 2H), 4.20 (s, 2H), 3.99 (d, 1H, J=13.7 Hz), 3.93 (d, 1H, J=13.7 Hz), 3.08-3.01 (m, 2H), 2.87-2.84 (m, 1H), 1.87 (s, 3H), 0.96 (t, 3H, J=7.2 Hz), 0.94-0.89 (m, 1H), 0.81-0.69 (m, 2H), 0.62-0.56 (m, 1H).

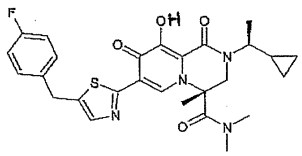
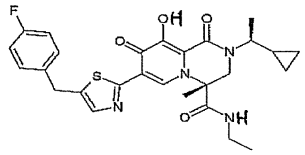
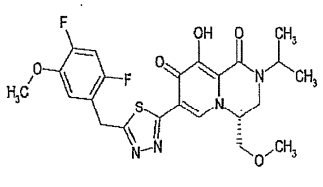
CUADRO 1-75

No.	Fórmula estructural	sal	^{1}H-NMR
268		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.70 (br s, 1H), 8.61 (s, 1H), 7.69 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.20 (s, 2H), 4.07-4.01 (m, 1H), 3.92 (d, 1H, J=13.2 Hz), 3.87-3.82 (m, 2H), 3.80 (d, 1H, J=13.2 Hz), 3.50-3.42 (m, 1H), 2.89-2.84 (m, 1H), 2.08-2.00 (m, 2H), 1.89 (s, 3H), 0.91-0.85 (m, 1H), 0.82-0.73 (m, 2H), 0.67-0.61 (m, 1H).
269		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.18 (br s, 1H), 8.67 (s, 1H), 7.42-7.38 (m, 2H), 7.20-7.14 (m, 2H), 4.46 (s, 2H), 3.83 (d, 1H, J=13.7 Hz), 3.74 (d, 1H, J=13.7 Hz), 3.64 (d, 1H, J=11.8 Hz), 3.62 (d, 1H, J=11.8 Hz), 3.60-3.44 (m, 3H), 1.59 (s, 3H), 1.15 (t, 3H, J=7.2 Hz).
270		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.69 (br s, 1H), 8.75 (s, 1H), 7.41-7.38 (m, 2H), 7.20-7.15 (m, 2H), 4.53 (d, 1H, J=13.7 Hz), 4.46 (s, 2H), 4.30 (d, 1H, J=13.7 Hz), 3.68-3.59 (m, 1H), 3.51 (d, 1H, J=10.4 Hz), 3.48-3.43 (m, 2H), 3.20 (s, 3H), 1.35 (s, 3H), 1.19 (t, 3H, J=7.1 Hz).
271		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.69 (br s, 1H), 8.61 (s, 1H), 7.69 (s, 1H), 7.34-7.31 (m, 2H), 7.16-7.12 (m, 2H), 4.20 (s, 2H), 4.17-4.15 (m, 1H), 4.02 (d, 1H, J=13.5 Hz), 4.00-3.87 (m, 2H), 3.89 (d, 1H, J=13.5 Hz), 3.65-3.63 (m, 1H), 3.54-3.44 (m, 2H), 2.10-2.06 (m, 2H), 1.91 (s, 3H), 1.10 (t, 3H, J=7.1 Hz).

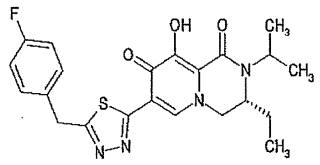
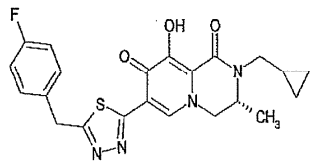
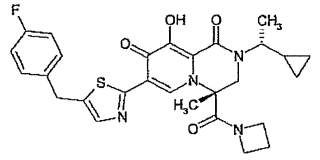
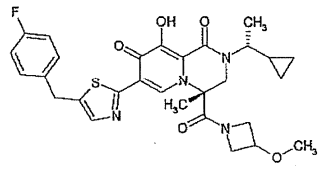
CUADRO 1-76

No.	Fórmula estructural	sal	^{1}H-NMR
272		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.65 (br s, 1H), 8.66 (s, 1H), 7.64 (s, 1H), 7.47-7.41 (m, 1H), 7.24 (dt, 1H, J=14.0, 5.0 Hz), 7.06 (td, 1H, J=8.5, 2.3 Hz), 5.10-5.03 (m, 1H), 4.80-4.73 (m, 1H), 4.20 (s, 2H), 4.18-4.04 (m, 2H), 3.98-3.85 (m, 1H), 3.87-3.71 (m, 3H), 3.61-3.53 (m, 1H), 3.15 (s, 1.5H), 3.08 (s, 1.5H), 2.66-2.58 (m, 2H), 1.15-1.11 (m, 6H).
273		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.83 (br s, 1H), 8.59 (s, 1H), 7.70 (s, 1H), 7.35-7.32 (m, 2H), 7.17-7.13 (m, 2H), 4.21 (s, 2H), 4.21-4.17 (m, 1H), 4.14 (d, 1H, J=13.7 Hz), 3.93-3.76 (m, 5H), 2.16-2.08 (m, 2H), 1.97 (s, 3H), 1.24 (d, 3H, J=6.8 Hz), 1.13-1.10 (m, 1H), 0.64-0.58 (m, 1H), 0.43-0.38 (m, 2H), 0.20-0.15 (m, 1H).
274		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.81 (br s, 1H), 8.58 (s, 1H), 7.70 (s, 1H), 7.35-7.32 (m, 2H), 7.17-7.13 (m, 2H), 4.21 (s, 2H), 4.21-4.14 (m, 3H), 4.06-4.00 (m, 1H), 3.87-3.64 (m, 4H), 3.15 (s, 3H), 1.98 (s, 3H), 1.24 (d, 3H, J=6.6 Hz), 1.13-1.09 (m, 1H), 0.61-0.57 (m, 1H), 0.49-0.36 (m, 2H), 0.15-0.07 (m, 1H).

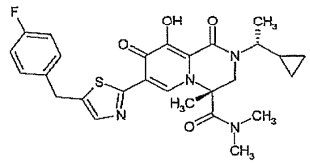
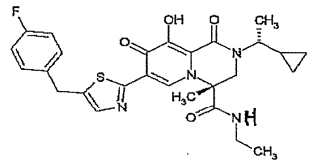
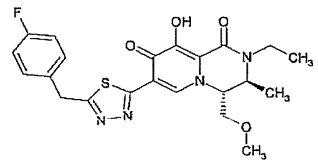
CUADRO 1-77

No.	Fórmula estructural	sal	^{1}H-NMR
275		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.84 (br s, 1H), 8.48 (s, 1H), 7.69 (s, 1H), 7.35-7.32 (m, 2H), 7.17-7.13 (m, 2H), 4.31 (d, 1H, J=14.3 Hz), 4.21 (s, 2H), 3.93 (d, 1H, J=14.3 Hz), 3.83-3.75 (m, 1H), 2.98 (br s, 6H), 2.05 (s, 3H), 1.25 (d, 3H, J=6.8 Hz), 1.10-1.03 (m, 1H), 0.64-0.58 (m, 1H), 0.42-0.33 (m, 2H), 0.12-0.08 (m, 1H).
276		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.86 (br s, 1H), 8.52 (s, 1H), 8.21 (t, 1H, J=5.4 Hz), 7.69 (s, 1H), 7.36-7.31 (m, 2H), 7.18-7.13 (m, 2H), 4.29 (d, 1H, J=13.7 Hz), 4.21 (s, 2H), 3.87 (d, 1H, J=13.7 Hz), 3.81-3.73 (m, 1H), 3.20-3.14 (m, 1H), 3.02-2.96 (m, 1H), 1.94 (s, 3H), 1.24 (d, 3H, J=6.8 Hz), 1.13-1.07 (m, 1H), 1.01 (t, 3H, J=7.2 Hz), 0.62-0.57 (m, 1H), 0.37-0.31 (m, 2H), 0.18-0.12 (m, 1H).
277		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.82 (br s, 1H), 8.80 (s, 1H), 7.38-7.32 (m, 2H), 4.99-4.97 (m, 1H), 4.80-4.74 (m, 1H), 4.46 (s, 2H), 3.84 (dd, 1H, J=13.5, 4.2 Hz), 3.83 (s, 3H), 3.75 (dd, 1H, J=13.5, 1.2 Hz), 3.63 (dd, 1H, J=10.3, 5.8 Hz), 3.57 (dd, 1H, J=10.3, 7.7 Hz), 3.25 (s, 3H), 1.17 (d, 3H, J=2.0 Hz), 1.15 (d, 3H, J=2.0 Hz).

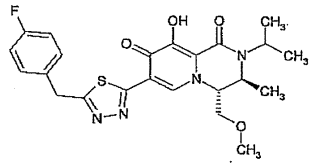
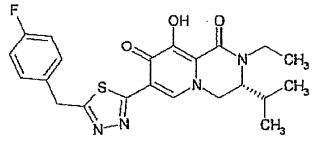
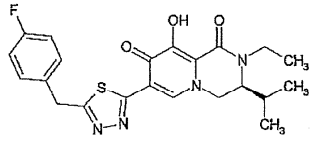
CUADRO 1-78

No.	Fórmula estructural	sal	^{1}H-NMR
278		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.45 (br s, 1H), 8.98 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.71-4.67 (m, 1H), 4.56-4.49 (m, 1H), 4.47 (s, 2H), 4.30-4.25 (m, 1H), 3.93-3.90 (m, 1H), 1.65-1.61 (m, 1H), 1.46-1.38 (m, 1H), 1.29 (d, 3H, J=2.4 Hz), 1.27 (d, 3H, J=2.0 Hz), 0.92 (t, 3H, J=7.5 Hz).
279		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.60 (br s, 1H), 8.84 (s, 1H), 7.43-7.38 (m, 2H), 7.20-7.15 (m, 2H), 4.50-4.46 (m, 1H), 4.46 (s, 2H), 4.41 (dd, 1H, J=13.1, 3.6 Hz), 4.20-4.17 (m, 1H), 3.57 (dd, 1H, J=14.0, 7.1 Hz), 3.22 (dd, 1H, J=14.0, 7.0 Hz), 1.24 (d, 3H, J=6.5 Hz), 1.14-1.10 (m, 1H), 0.56-0.47 (m, 2H), 0.39-0.36 (m, 1H), 0.33-0.29 (m, 1H).
280		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.75 (br s, 1H), 8.61 (s, 1H), 7.70 (s, 1H), 7.35-7.32 (m, 2H), 7.18-7.13 (m, 2H), 4.21 (s, 2H), 4.21-4.13 (m, 2H), 3.86-3.73 (m, 5H), 2.14-2.06 (m, 2H), 1.96 (s, 3H), 1.20 (d, 3H, J=6.6 Hz), 1.15-1.07 (m, 1H), 0.64-0.58 (m, 1H), 0.45-0.38 (m, 2H), 0.23-0.20 (m, 1H).
281		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.74 (br s, 1H), 8.60 (s, 1H), 7.70 (s, 1H), 7.36-7.32 (m, 2H), 7.17-7.13 (m, 2H), 4.21 (s, 2H), 4.15-4.04 (m, 4H), 3.89-3.78 (m, 2H), 3.68-3.58 (m, 2H), 3.15 (s, 1.5H), 3.14 (s, 1.5H), 1.98 (s, 3H), 1.19-1.11 (m, 4H), 0.61-0.57 (m, 1H), 0.49-0.38 (m, 2H), 0.22-0.19 (m, 1H).

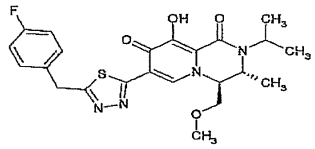
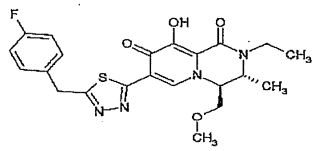
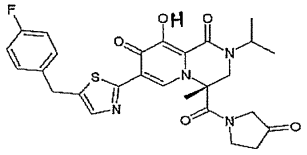
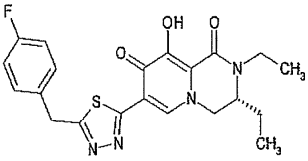
CUADRO 1-79

No.	Fórmula estructural	sal	^{1}H-NMR
282		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.84 (br s, 1H), 8.42 (s, 1H), 7.69 (s, 1H), 7.35-7.32 (m, 2H), 7.18-7.12 (m, 2H), 4.24 (d, 1H, J=14.3 Hz), 4.21 (s, 2H), 3.93 (d, 1H, J=14.3 Hz), 3.89-3.81 (m, 1H), 2.94 (br s, 6H), 1.99 (s, 3H), 1.19 (d, 3H, J=6.6 Hz), 1.15-1.09 (m, 1H), 0.63-0.58 (m, 1H), 0.48-0.39 (m, 2H), 0.26-0.22 (m, 1H).
283		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.77 (br s, 1H), 8.53 (s, 1H), 8.25 (t, 1H, J=5.4 Hz), 7.69 (s, 1H), 7.35-7.32 (m, 2H), 7.17-7.13 (m, 2H), 4.29 (d, 1H, J=13.9 Hz), 4.21 (s, 2H), 3.92 (d, 1H, J=13.9 Hz), 3.89-3.83 (m, 1H), 3.16-3.02 (m, 2H), 1.95 (s, 3H), 1.18 (d, 3H, J=6.8 Hz), 1.03-1.01 (m, 1H), 1.01 (t, 3H, J=7.2 Hz), 0.62-0.58 (m, 1H), 0.47-0.39 (m, 2H), 0.24-0.19 (m, 1H).
284		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.66 (br s, 1H), 8.82 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.83 (br t, 1H, J=6.6 Hz), 4.48 (s, 2H), 4.04 (q, 1H, J=6.2 Hz), 3.95-3.86 (m, 1H), 3.64 (dd, 1H, J=10.4, 5.3 Hz), 3.53 (dd, 1H, J=10.4, 7.9 Hz), 3.24 (s, 3H), 3.16-3.07 (m, 1H), 1.26 (d, 3H, J=6.6 Hz), 1.16 (t, 3H, J=7.1 Hz).

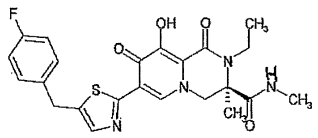
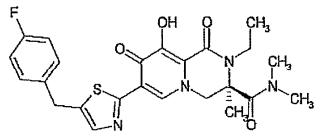
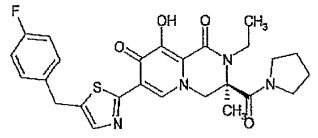
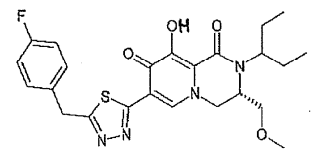
CUADRO 1-80

No.	Fórmula estructural	sal	^{1}H-NMR
285		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.67 (br s, 1H), 8.82 (s, 1H), 7.43-7.39 (m, 2H), 7.22-7.15 (m, 2H), 4.82 (br t, 1H, J=6.0 Hz), 4.65-4.58 (m, 1H), 4.48 (s, 2H), 4.16 (q, 1H, J=6.5 Hz), 3.60 (dd, 1H, J=10.3, 5.4 Hz), 3.49 (dd, 1H, J=10.3, 7.9 Hz), 3.24 (s, 3H), 1.27 (d, 3H, J=2.0 Hz), 1.26 (d, 3H, J=2.0 Hz), 1.21 (t, 3H, J=6.8 Hz).
286		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.53 (br s, 1H), 9.01 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.15 (m, 2H), 4.75 (d, 1H, J=13.8 Hz), 4.47 (s, 2H), 4.34 (dd, 1H, J=13.8, 4.3 Hz), 4.01 (td, 1H, J=13.8, 6.9 Hz), 3.74 (br t, 1H, J=5.0 Hz), 3.74 (td, 1H, J=13.8, 6.9 Hz), 1.92 (td, 1H, J=13.8, 6.9 Hz), 1.20 (t, 3H, J = 6.9 Hz), 0.99 (d, 3H, J=6.9 Hz), 0.79 (d, 3H, J=6.9 Hz).
287		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.53 (br s, 1H), 9.01 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.15 (m, 2H), 4.75 (d, 1H, J=13.8 Hz), 4.47 (s, 2H), 4.34 (dd, 1H, J=13.8, 4.3 Hz), 4.01 (td, 1H, J=13.8, 6.9 Hz), 3.74 (br t, 1H, J=5.0 Hz), 3.74 (td, 1H, J=13.8, 6.9 Hz), 1.92 (td, 1H, J=13.8, 6.9 Hz), 1.20 (t, 3H, J = 6.9 Hz), 0.99 (d, 3H, J=6.9 Hz), 0.79 (d, 3H, J=6.9 Hz).

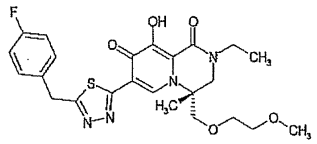
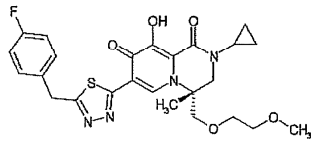
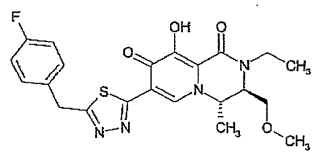
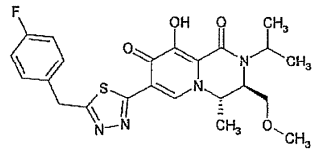
CUADRO 1-81

No.	Fórmula estructural	sal	^{1}H-NMR
288		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.67 (br s, 1H), 8.82 (s, 1H), 7.43-7.39 (m, 2H), 7.22-7.15 (m, 2H), 4.82 (br t, 1H, J=6.0 Hz), 4.65-4.58 (m, 1H), 4.48 (s, 2H), 4.16 (q, 1H, J=6.5 Hz), 3.60 (dd, 1H, J=10.3, 5.4 Hz), 3.49 (dd, 1H, J=10.3, 7.9 Hz), 3.24 (s, 3H), 1.27 (d, 3H, J=2.0 Hz), 1.26 (d, 3H, J=2.0 Hz), 1.21 (t, 3H, J=6.8 Hz).
289		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.66 (br s, 1H), 8.82 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.83 (br t, 1H, J=6.6 Hz), 4.48 (s, 2H), 4.04 (q, 1H, J=6.2 Hz), 3.95-3.86 (m, 1H), 3.64 (dd, 1H, J=10.4, 5.3 Hz), 3.53 (dd, 1H, J=10.4, 7.9 Hz), 3.24 (s, 3H), 3.16-3.07 (m, 1H), 1.26 (d, 3H, J=6.6 Hz), 1.16 (t, 3H, J=7.1 Hz).
290		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.86 (br s, 1H), 8.56 (s, 1H), 7.70 (s, 1H), 7.37-7.31 (m, 2H), 7.19-7.12 (m, 2H), 4.73-4.66 (m, 1H), 4.21 (s, 2H), 4.19-4.07 (m, 2H), 3.86-3.70 (m, 6H), 2.03 (s, 3H), 1.17 (d, 3H, J = 6.5 Hz), 1.10 (d, 3H, J=6.5 Hz).
291		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.53 (br s, 1H), 8.96 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.65 (d, 1H, J=13.5 Hz), 4.47 (s, 2H), 4.35 (dd, 1H, J=13.5, 3.8 Hz), 3.92-3.84 (m, 2H), 3.24-3.16 (m, 1H), 1.72-1.66 (m, 1H), 1.51-1.41 (m, 1H), 1.20 (t, 3H, J=7.3 Hz), 0.92 (t, 3H, J=7.5 Hz).

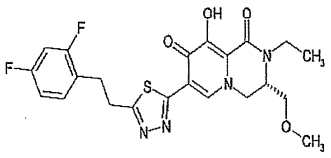
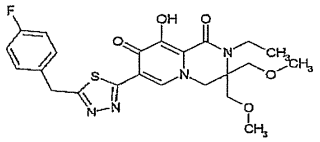
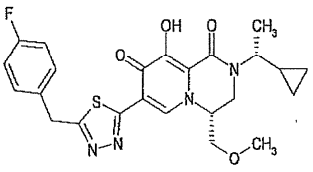
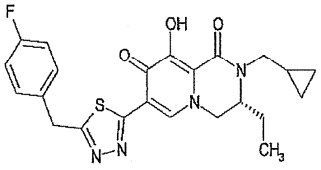
CUADRO 1-82

No.	Fórmula estructural	sal	^{1}H-NMR
292		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.40 (br s, 1H), 8.52 (s, 1H), 8.09-8.05 (m, 1H), 7.65 (s, 1H), 7.34-7.29 (m, 2H), 7.16-7.10 (m, 2H), 4.67 (d, 1H, J=13.5 Hz), 4.37 (d, 1H, J=13.5 Hz), 4.19 (s, 2H), 3.76-3.68 (m, 1H), 3.38-3.29 (m, 1H), 2.54 (d, 3H, J=4.4 Hz), 1.65 (s, 3H), 1.51 (t, 3H, J=7.1 Hz).
293		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.40 (br s, 1H), 8.68 (s, 1H), 7.66 (s, 1H), 7.34-7.30 (m, 2H), 7.16-7.11 (m, 2H), 4.86 (d, 1H, J=14.1 Hz), 4.46 (d, 1H, J=14.1 Hz), 4.19 (s, 2H), 3.78-3.69 (m, 1H), 3.18-3.09 (m, 1H), 2.99 (br s, 6H), 1.71 (s, 3H), 1.19 (t, 3H, J=7.1 Hz).
294		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.42 (br s, 1H), 8.69 (s, 1H), 7.65 (s, 1H), 7.34-7.29 (m, 2H), 7.16-7.11 (m, 2H), 4.86 (d, 1H, J=13.9 Hz), 4.46 (d, 1H, J=13.9 Hz), 4.30-4.03 (m, 1H), 4.19 (s, 2H), 3.78-3.68 (m, 2H), 3.46-3.17 (m, 3H), 1.98-1.78 (m, 4H), 1.73 (s, 3H), 1.17 (t, 3H, J=7.1 Hz).
295		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.46 (br s, 1H), 8.84 (s, 1H), 7.43-7.39 (m, 2H), 7.20-7.15 (m, 2H), 4.68 (d, 1H, J=13.5 Hz), 4.46 (s, 2H), 4.36 (dd, 1H, J=13.5, 3.7 Hz), 4.08-4.00 (m, 2H), 3.49 (dd, 1H, J=10.2, 3.9 Hz), 3.41 (dd, 1H, J=10.2, 7.0 Hz), 3.17 (s, 3H), 1.77-1.59 (m, 4H), 0.90 (t, 3H, J=7.3 Hz), 0.85 (t, 3H, J=7.3 Hz).

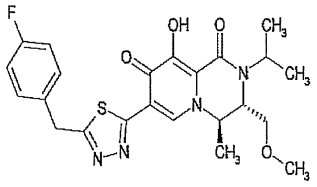
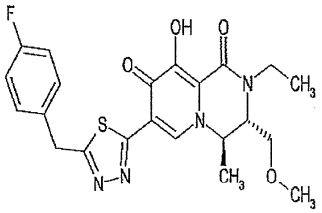
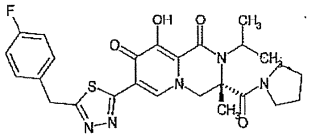
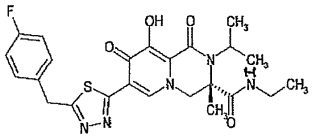
CUADRO 1-83

No.	Fórmula estructural	sal	^{1}H-NMR
296		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.19 (br s, 1H), 8.71 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.47 (s, 2H), 3.86-3.76 (m, 3H), 3.70 (d, 1H, J=10.4 Hz), 3.63-3.45 (m, 4H), 3.35-3.33 (m, 2H), 3.11 (s, 3H), 1.64 (s, 3H), 1.17 (t, 3H, J=7.2 Hz).
297		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.21 (br s, 1H), 8.71 (s, 1H), 7.42-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.47 (s, 2H), 3.80-3.63 (m, 4H), 3.51-3.44 (m, 2H), 3.35-3.33 (m, 2H), 3.12 (s, 3H), 2.95-2.90 (m, 1H), 1.62 (s, 3H), 0.93-0.76 (m, 4H).
298		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.51 (br s, 1H), 8.93 (s, 1H), 7.42-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.91 (q, 1H, J=6.8 Hz), 4.48 (s, 2H), 4.04-3.95 (m, 2H), 3.52 (dd, 1H, J=10.3, 5.2 Hz), 3.46 (dd, 1H, J=10.3, 6.5 Hz), 3.22 (s, 3H), 3.20-3.13 (m, 1H), 1.42 (d, 3H, J=6.6 Hz), 1.19 (t, 3H, J=7.1 Hz).
299		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.48 (br s, 1H), 8.95 (s, 1H), 7.42-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.95 (q, 1H, J=6.5 Hz), 4.58-4.51 (m, 1H), 4.48 (s, 2H), 4.07-4.04 (m, 1H), 3.50 (dd, 1H, J=10.5, 4.1 Hz), 3.36 (dd, 1H, J=10.5, 7.9 Hz), 3.22 (s, 3H), 1.39 (d, 3H, J=6.8 Hz), 1.29 (d, 3H, J=5.0 Hz), 1.27 (d, 3H, J=5.0 Hz).

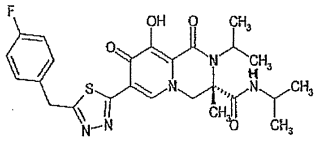
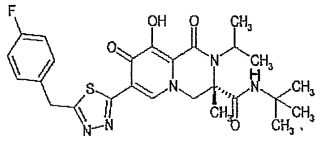
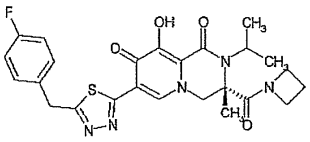
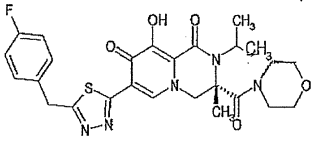
CUADRO 1-84

No.	Fórmula estructural	sal	^{1}H-NMR
300		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.50 (br s, 1H), 8.82 (s, 1H), 7.39 (dd, 1H, J=15.3, 8.7 Hz), 7.22-7.16 (m, 1H), 7.02 (td, 1H, J=8.7, 2.4 Hz), 4.63 (d, 1H, J=13.3 Hz), 4.42 (dd, 1H, J=13.3, 4.3 Hz), 4.17-4.13 (m, 1H), 3.87 (td, 1H, J=14.0, 7.1 Hz), 3.56-3.49 (m, 2H), 3.40 (t, 2H, J=7.5 Hz), 3.32-3.25 (m, 1H), 3.22 (s, 3H), 3.09 (t, 2H, J=7.5 Hz), 1.21 (t, 3H, J=7.1 Hz).
301		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.61 (br s, 1H), 8.78 (s, 1H), 7.42-7.39 (m, 2H), 7.20-7.16 (m, 2H), 4.51 (s, 2H), 4.47 (s, 2H), 3.65-3.53 (m, 6H), 3.26 (s, 6H), 1.19 (t, 3H, J=7.1 Hz).
302		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (br s, 1H), 8.80 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.15 (m, 2H), 4.99-4.95 (m, 1H), 4.46 (s, 2H), 3.99-3.84 (m, 3H), 3.63 (dd, 1H, J=10.3, 5.7 Hz), 3.57 (dd, 1H, J=10.3, 7.7 Hz), 3.24 (s, 3H), 1.22 (d, 3H, J=7.0 Hz), 1.08-1.00 (m, 1H), 0.61-0.55 (m, 1H), 0.47-0.36 (m, 2H), 0.23-0.18 (m, 1H).
303		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.50 (br s, 1H), 8.97 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.69 (d, 1H, J=13.3 Hz), 4.48 (s, 2H), 4.38 (dd, 1H, J=13.3, 3.4 Hz), 3.95-3.93 (m, 1H), 3.69 (dd, 1H, J=13.9, 7.1 Hz), 3.16 (dd, 1H, J=13.9 7.2 Hz), 1.79-1.72 (m, 1H), 1.48-1.40 (m, 1H), 1.19-1.12 (m, 1H), 0.93 (t, 3H, J=7.4 Hz), 0.55-0.48 (m, 2H), 0.42-0.37 (m, 1H), 0.34-0.30 (m, 1H).

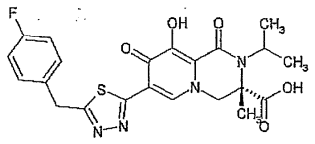
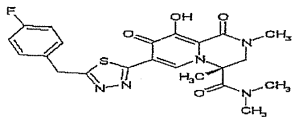
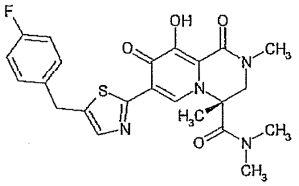
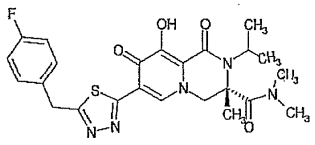
CUADRO 1-85

No.	Fórmula estructural	sal	^{1}H-NMR
304		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.48 (br s, 1H), 8.95 (s, 1H), 7.42-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.95 (q, 1H, J=6.5 Hz), 4.58-4.51 (m, 1H), 4.48 (s, 2H), 4.07-4.04 (m, 1H), 3.50 (dd, 1H, J=10.5, 4.1 Hz), 3.36 (dd, 1H, J=10.5, 7.9 Hz), 3.22 (s, 3H), 1.39 (d, 3H, J=6.8 Hz), 1.29 (d, 3H, J=5.0 Hz), 1.27 (d, 3H, J=5.0 Hz).
305		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.51 (br s, 1H), 8.93 (s, 1H), 7.42-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.91 (q, 1H, J=6.8 Hz), 4.48 (s, 2H), 4.04-3.95 (m, 2H), 3.52 (dd, 1H, J=10.3, 5.2 Hz), 3.46 (dd, 1H, J=10.3, 6.5 Hz), 3.22 (s, 3H), 3.20-3.13 (m, 1H), 1.42 (d, 3H, J=6.6 Hz), 1.19 (t, 3H, J=7.1 Hz).
306		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.70 (br s, 1H), 8.86 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.80 (d, 1H, J = 14.0 Hz), 4.49 (d, 1H, J = 14.0 Hz), 4.47 (s, 2H), 4.11-3.06 (m, 4H), 3.60 (sep, 1H, J = 6.6 Hz), 2.06-1.63 (m, 4H), 1.73 (s, 3H), 1.46 (d, 3H, J = 6.6 Hz), 1.43 (d, 3H, J = 6.6 Hz).
307		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.65 (br s, 1H), 8.74 (s, 1H), 8.31 (t, 1H, J = 5.5 Hz), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.58 (d, 1H, J = 13.5 Hz), 4.48 (d, 1H, J = 13.5 Hz), 4.47 (s, 2H), 3.53 (sep, 1H, J = 6.6 Hz), 3.20-3.09 (m, 2H), 1.58 (s, 3H), 1.48 (d, 3H, J = 6.6 Hz), 1.41 (d, 3H, J = 6.6 Hz), 1.01 (t, 3H, J = 7.2 Hz).

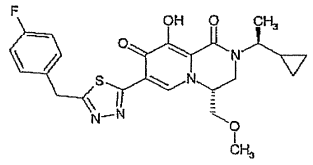
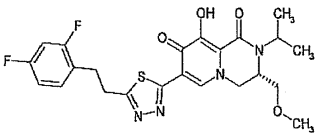
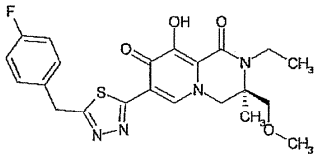
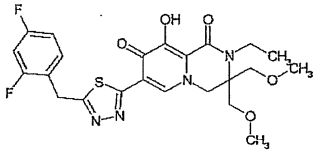
CUADRO 1-86

No.	Fórmula estructural	sal	^{1}H-NMR
308		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.68 (br s, 1H), 8.74 (s, 1H), 8.11 (d, 1H, J = 7.7 Hz), 7.45-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.61 (d, 1H, J = 14.0 Hz), 4.49 (d, 1H, J = 14.0 Hz), 4.47 (s, 2H), 3.91 (sep, 1H, J = 6.6 Hz), 3.48 (sep, 1H, J = 6.6 Hz), 1.55 (s, 3H), 1.51 (d, 3H, J = 6.6 Hz), 1.41 (d, 3H, J = 6.6 Hz), 1.09 (d, 3H, J = 6.6 Hz), 1.06 (d, 3H, J = 6.6 Hz).
309		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (br s, 1H), 8.75 (s, 1H), 7.77 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.15 (m, 2H), 4.67 (d, 1H, J = 13.5 Hz), 4.49 (d, 1H, J = 13.5 Hz), 4.47 (s, 2H), 3.40 (sep, 1H, J = 6.7 Hz), 1.54 (d, 3H, J = 6.7 Hz), 1.50 (s, 3H), 1.41 (d, 3H, J = 6.7 Hz), 1.29 (s, 9H).
310		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.66 (br s, 1H), 8.85 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.68-3.76 (m, 4H), 4.64 (d, 1H, J = 13.9 Hz), 4.47 (s, 2H), 4.46 (d, 1H, J = 13.9 Hz), 3.69 (sep, 1H, J = 6.7 Hz), 2.28-2.15 (m, 2H), 1.66 (s, 3H), 1.44 (d, 3H, J = 6.7 Hz), 1.43 (d, 3H, J = 6.7 Hz).
311		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.67 (br s, 1H), 8.81 (s, 1H), 7.45-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.71 (d, 1H, J = 14.0 Hz), 4.58 (d, 1H, J = 14.0 Hz), 4.47 (s, 2H), 3.75-3.40 (m, 9H), 1.66 (s, 3H), 1.53 (d, 3H, J = 6.6 Hz), 1.42 (d, 3H, J = 6.6 Hz).

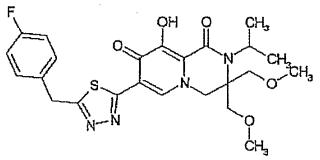
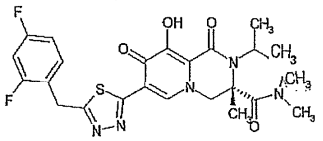
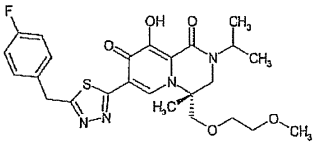
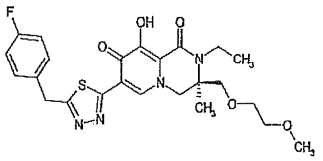
CUADRO 1-87

No.	Fórmula estructural	sal	^{1}H-NMR
312		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.99 (br s, 1H), 12.50 (br s, 1H), 8.83 (s, 1H), 7.45-7.37 (m, 2H), 7.23-7.13 (m, 2H), 4.78 (d, 1H, J = 14.0 Hz), 4.49 (d, 1H, J = 14.0 Hz), 4.47 (s, 2H), 3.85 (sep, 1H, J = 6.8 Hz), 1.66 (s, 3H), 1.49 (d, 3H, J = 6.8 Hz), 1.45 (d, 3H, J = 6.8 Hz).
313		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.88 (br s, 1H), 8.55 (s, 1H), 7.45-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.48 (s, 2H), 4.21 (d, 1H, J = 14.0 Hz), 3.96 (d, 1H, J = 14.0 Hz), 3.07 (s, 3H), 2.91 (s, 6H), 1.98 (s, 3H).
314		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (br s, 1H), 8.42 (s, 1H), 7.69 (s, 1H), 7.36-7.30 (m, 2H), 7.18-7.11 (m, 2H), 4.21 (s, 2H), 4.20 (d, 1H, J = 13.9 Hz), 3.91 (d, 1H, J = 13.9 Hz), 3.07 (s, 3H), 2.89 (s, 6H), 1.92 (s, 3H).
315		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.70 (br s, 1H), 8.84 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.16 (m, 2H), 4.80 (d, 1H, J = 13.9 Hz), 4.53 (d, 1H, J = 13.9 Hz), 4.47 (s, 2H), 3.45 (sep, 1H, J = 6.6 Hz), 3.08 (s, 6H), 1.65 (s, 3H), 1.49 (d, 3H, J = 6.6 Hz), 1.42 (d, 3H, J = 6.6 Hz).

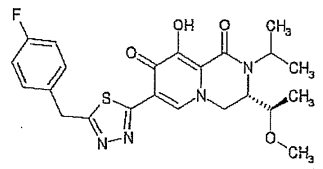
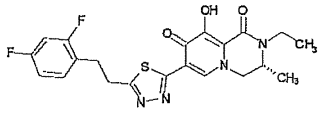
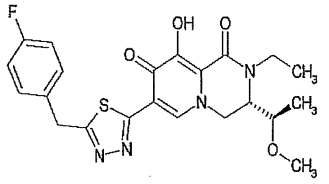
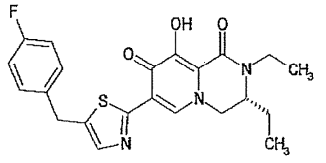
CUADRO 1-88

No.	Fórmula estructural	sal	^{1}H-NMR
316		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.79 (br s, 1H), 8.80 (s, 1H), 7.45-7.39 (m, 2H), 7.23-7.15 (m, 2H), 5.06-4.97 (m, 1H), 4.48 (s, 2H), 3.94-3.91 (m, 2H), 3.90-3.80 (m, 1H), 3.72-3.58 (m, 2H), 3.26 (s, 3H), 1.23 (d, 3H, J = 6.8 Hz), 1.18-1.07 (m, 1H), 0.66-0.57 (m, 1H), 0.50-0.37 (m, 2H), 0.31-0.20 (m, 1H).
317		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.48 (br s, 1H), 8.84 (s, 1H), 7.44-7.36 (m, 1H), 7.23-7.15 (m, 1H), 7.06-6.98 (m, 1H), 4.66 (dd, 1H, J = 13.6, 1.4 Hz), 4.48 (sep, 1H, J = 6.8 Hz), 4.35 (dd, 1H, J = 13.6, 3.6 Hz), 4.24-4.17 (m, 1H), 3.50 (dd, 1H, J = 10.4, 4.2 Hz), 3.44-3.37 (m, 3H), 3.22 (s, 3H), 3.09 (t, 2H, J = 7.5 Hz), 1.30 (d, 3H, J = 6.8 Hz), 1.29 (d, 3H, J = 6.8 Hz).
318		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.71 (br s, 1H), 8.76 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.15 (m, 2H), 4.55 (d, 1H, J = 13.5 Hz), 4.47 (s, 2H), 4.31 (d, 1H, J = 13.5 Hz), 3.71-3.59 (m, 1H), 3.56-3.42 (m, 3H), 3.21 (s, 3H), 1.37 (s, 3H), 1.20 (t, 3H, J = 7.1 Hz).
319		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.63 (br s, 1H), 8.77 (s, 1H), 7.58-7.48 (m, 1H), 7.33-7.25 (m, 1H), 7.16-7.08 (m, 1H), 4.52 (s, 2H), 4.49 (s, 2H), 3.63 (d, 2H, J = 10.6 Hz), 3.58 (q, 2H, J = 7.1 Hz), 3.54 (d, 2H, J = 10.6 Hz), 3.26 (s, 6H), 1.19 (t, 3H, J = 7.1 Hz).

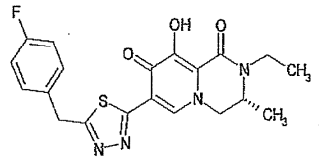
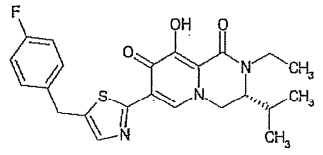
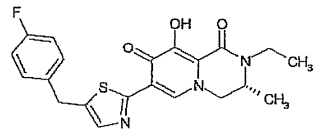
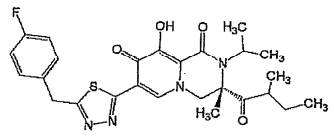
CUADRO 1-89

No.	Fórmula estructural	sal	^{1}H-NMR
320		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.74 (br s, 1H), 8.74 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.14 (m, 2H), 4.50 (s, 2H), 4.47 (s, 2H), 3.94 (sep, 1H, J = 6.6 Hz), 3.66 (d, 2H, J = 10.6 Hz), 3.51 (d, 2H, J = 10.6 Hz), 3.27 (s, 6H), 1.45 (d, 6H, J = 6.6 Hz).
321		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.71 (br s, 1H), 8.83 (s, 1H), 7.58-7.50 (m, 1H), 7.33-7.26 (m, 1H), 7.15-7.08 (m, 1H), 4.80 (d, 1H, J = 14.0 Hz), 4.54 (d, 1H, J = 14.0 Hz), 4.49 (s, 2H), 3.45 (sep, 1H, J = 6.7 Hz), 3.07 (s, 6H), 1.65 (s, 3H), 1.49 (d, 3H, J = 6.7 Hz), 1.42 (d, 3H, J = 6.7 Hz).
322		HCl	^{1}H-NMR (DMSO-d_6) δ : 13.25 (br s, 1H), 8.71 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.79 (sep, 1H, J = 6.8 Hz), 4.47 (s, 2H), 3.80-3.73 (m, 2H), 3.71-3.64 (m, 2H), 3.55-3.43 (m, 2H), 3.37-3.31 (m, 2H), 3.11 (s, 3H), 1.65 (s, 3H), 1.18 (d, 3H, J = 6.8 Hz), 1.18 (d, 3H, J = 6.8 Hz).
323		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.69 (br s, 1H), 8.73 (s, 1H), 7.44-7.38 (m, 2H), 7.23-7.15 (m, 2H), 4.55 (d, 1H, J = 13.5 Hz), 4.47 (s, 2H), 4.31 (d, 1H, J = 13.5 Hz), 3.71-3.46 (m, 4H), 3.46-3.42 (m, 2H), 3.29-3.24 (m, 2H), 3.07 (s, 3H), 1.37 (s, 3H), 1.20 (t, 3H, J = 7.1 Hz).

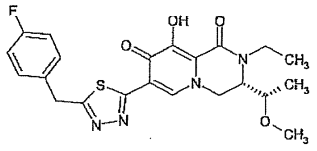
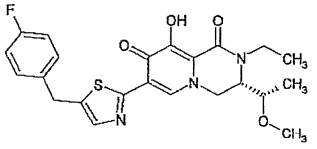
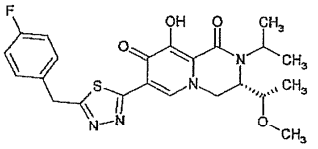
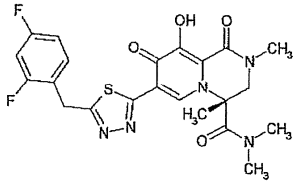
CUADRO 1-90

No.	Fórmula estructural	sal	^{1}H-NMR
324		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.52 (br s, 1H), 8.91 (s, 1H), 7.44-7.36 (m, 2H), 7.22-7.14 (m, 2H), 4.82 (d, 1H, J = 13.5 Hz), 4.47 (s, 2H), 4.35 (sep, 1H, J = 6.8 Hz), 4.30 (dd, 1H, J = 13.5, 4.5 Hz), 4.01-3.96 (m, 1H), 3.64-3.55 (m, 1H), 3.05 (s, 3H), 1.35 (d, 3H, J = 6.8 Hz), 1.33 (d, 3H, J = 6.8 Hz), 1.19 (d, 3H, J = 6.2 Hz).
325		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.64 (br s, 1H), 8.83 (s, 1H), 7.44-7.35 (m, 1H), 7.23-7.15 (m, 1H), 7.05-6.98 (m, 1H), 4.50-4.37 (m, 2H), 4.16-4.07 (m, 1H), 3.88-3.76 (m, 1H), 3.40 (t, 2H, J = 7.5 Hz), 3.30-3.19 (m, 1H), 3.10 (t, 2H, J = 7.5 Hz), 1.24 (d, 3H, J = 6.6 Hz), 1.20 (t, 3H, J = 7.2 Hz).
326		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.50 (br s, 1H), 8.91 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.15 (m, 2H), 4.80 (d, 1H, J = 13.5 Hz), 4.47 (s, 2H), 4.36 (dd, 1H, J = 13.5, 4.6 Hz), 4.00-3.87 (m, 2H), 3.66-3.58 (m, 1H), 3.31-3.18 (m, 1H), 3.08 (s, 3H), 1.21 (t, 3H, J = 7.1 Hz), 1.16 (d, 3H, J = 6.4 Hz).
327		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.42 (br s, 1H), 8.76 (s, 1H), 7.67 (s, 1H), 7.36-7.30 (m, 2H), 7.19-7.11 (m, 2H), 4.61 (d, 1H, J = 13.2 Hz), 4.33 (dd, 1H, J = 13.2, 3.7 Hz), 4.20 (s, 2H), 3.95-3.83 (m, 1H), 3.88-3.80 (m, 1H), 3.22-3.11 (m, 1H), 1.74-1.62 (m, 1H), 1.50-1.36 (m, 1H), 1.20 (t, 3H, J = 7.2 Hz), 0.91 (t, 3H, J = 7.4 Hz).

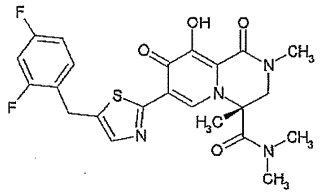
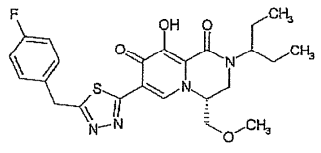
CUADRO 1-91

No.	Fórmula estructural	sal	^{1}H-NMR
328		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.62 (br s, 1H), 8.84 (s, 1H), 7.45-7.37 (m, 2H), 7.23-7.14 (m, 2H), 4.49-4.35 (m, 2H), 4.47 (s, 2H), 4.15-4.07 (m, 1H), 3.87-3.75 (m, 1H), 3.31-3.18 (m, 1H), 1.26-1.14 (m, 6H).
329		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.33 (br s, 1H), 8.82 (s, 1H), 7.67 (s, 1H), 7.37-7.30 (m, 2H), 7.18-7.11 (m, 2H), 4.71 (d, 1H, J = 13.9 Hz), 4.32 (dd, 1H, J = 13.9, 4.4 Hz), 4.20 (s, 2H), 4.07-3.94 (m, 1H), 3.75-3.69 (m, 1H), 3.16-3.04 (m, 1H), 1.97-1.85 (m, 1H), 1.20 (t, 3H, J = 7.1 Hz), 0.98 (d, 3H, J = 6.8 Hz), 0.78 (d, 3H, J = 6.8 Hz).
330		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.52 (br s, 1H), 8.66 (s, 1H), 7.67 (s, 1H), 7.37-7.30 (m, 2H), 7.19-7.11 (m, 2H), 4.46-4.33 (m, 2H), 4.20 (s, 2H), 4.14-4.04 (m, 1H), 3.86-3.75 (m, 1H), 3.29-3.18 (m, 1H), 1.22 (d, 3H, J = 6.6 Hz), 1.19 (t, 3H, J = 7.2 Hz).
331		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.68 (br s, 1H), 8.83 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.77 (d, 1H, J = 13.7 Hz), 4.55 (d, 1H, J = 13.7 Hz), 4.47 (s, 2H), 4.16-3.03 (m, 5H), 3.44 (sep, 1H, J = 6.6 Hz), 1.63 (s, 3H), 1.49 (d, 3H, J = 6.6 Hz), 1.42 (d, 3H, J = 6.6 Hz), 1.09-1.00 (m, 3H).

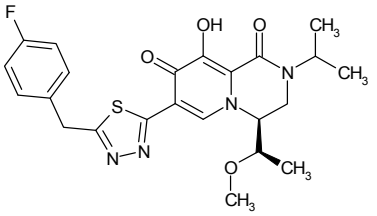
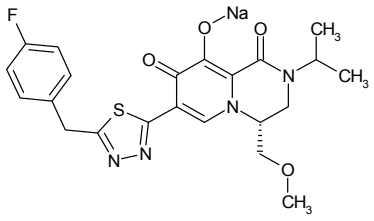
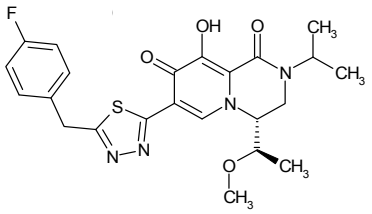
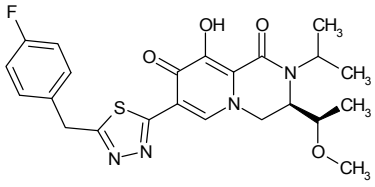
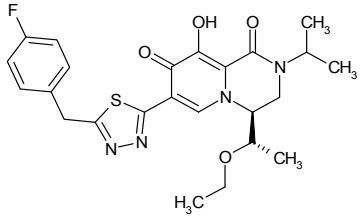
CUADRO 1-92

No.	Fórmula estructural	sal	^{1}H-NMR
332		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.50 (br s, 1H), 8.95 (s, 1H), 7.44–7.36 (m, 2H), 7.22–7.15 (m, 2H), 4.69 (dd, 1H, J = 14.0, 1.5 Hz), 4.47 (s, 2H), 4.39 (dd, 1H, J = 14.0, 4.2 Hz), 4.04–3.98 (m, 1H), 3.97–3.92 (m, 1H), 3.51–3.43 (m, 1H), 3.26–3.18 (m, 1H), 3.18 (s, 3H), 1.19 (t, 3H, J = 7.2 Hz), 1.10 (d, 3H, J = 6.2 Hz).
333		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.76 (s, 1H), 7.67 (s, 1H), 7.36–7.30 (m, 2H), 7.18–7.11 (m, 2H), 4.64 (dd, 1H, J = 13.6, 1.5 Hz), 4.37 (dd, 1H, J = 13.6, 4.0 Hz), 4.20 (s, 2H), 4.06–3.97 (m, 1H), 3.95–3.90 (m, 1H), 3.51–3.40 (m, 1H), 3.27–3.19 (m, 1H), 3.19 (s, 3H), 1.19 (t, 3H, J = 6.8 Hz), 1.08 (d, 3H, J = 6.4 Hz).
334		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.47 (br s, 1H), 8.96 (s, 1H), 7.44–7.38 (m, 2H), 7.22–7.15 (m, 2H), 4.68 (dd, 1H, J = 13.9, 1.3 Hz), 4.47 (s, 2H), 4.35 (dd, 1H, J = 13.9, 3.5 Hz), 4.14–4.06 (m, 1H), 3.98–3.93 (m, 1H), 3.41 (sep, 1H, J = 6.7 Hz), 3.24 (s, 3H), 1.39 (d, 3H, J = 6.7 Hz), 1.34 (d, 3H, J = 6.7 Hz), 1.02 (d, 3H, J = 6.3 Hz).
335		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.85 (br s, 1H), 8.54 (s, 1H), 7.58–7.50 (m, 1H), 7.33–7.25 (m, 1H), 7.15–7.08 (m, 1H), 4.49 (s, 2H), 4.21 (d, 1H, J = 13.9 Hz), 3.97 (d, 1H, J = 13.9 Hz), 3.07 (s, 3H), 2.91 (s, 6H), 1.97 (s, 3H).

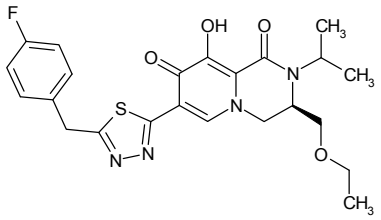
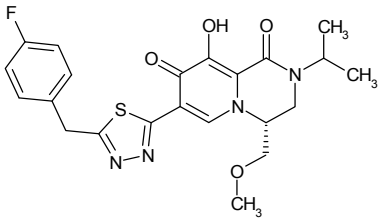
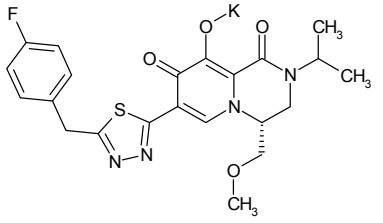
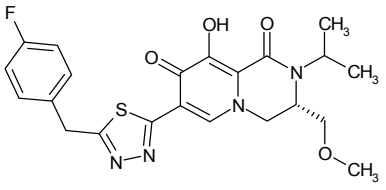
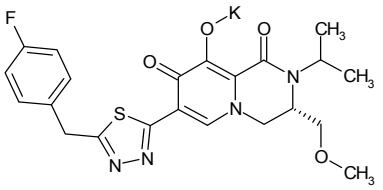
CUADRO 1-93

No.	Fórmula estructural	sal	^{1}H-NMR
336		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (br s, 1H), 8.46 (s, 1H), 7.69 (s, 1H), 7.50-7.42 (m, 1H), 7.29-7.21 (m, 1H), 7.11-7.05 (m, 1H), 4.22 (s, 2H), 4.21 (d, 1H, J = 14.0 Hz), 3.93 (d, 1H, J = 14.0 Hz), 3.07 (s, 3H), 2.89 (s, 6H), 1.93 (s, 3H).
337		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.86 (br s, 1H), 8.83 (s, 1H), 7.45-7.39 (m, 2H), 7.23-7.16 (m, 2H), 5.02-4.94 (m, 1H), 4.47 (s, 2H), 4.40-4.29 (m, 1H), 3.83-3.56 (m, 4H), 3.26 (s, 3H), 1.64-1.43 (m, 4H), 0.92-0.78 (m, 6H).

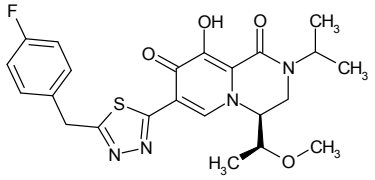
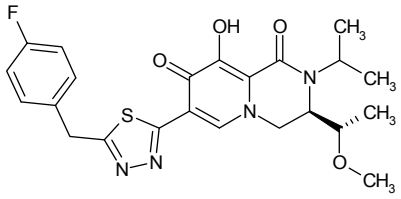
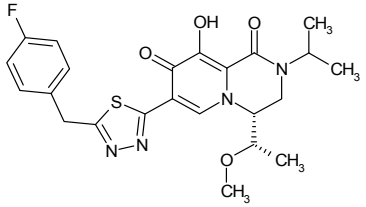
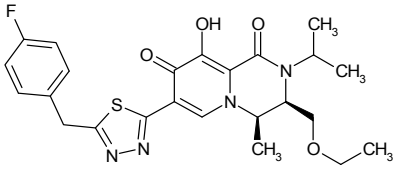
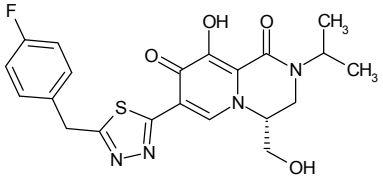
CUADRO 1-94

No.	fórmula estructural	sal	^{1}H- NMR
338		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.92 (s, 1H), 7.44-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.78 (quint, 1H, J = 6.9 Hz), 4.71 (ddd, 1H, J = 6.4, 4.0, 1.6 Hz), 4.47 (s, 2H), 3.87 (dd, 1H, J = 13.7, 1.6 Hz), 3.78 (dd, 1H, J = 13.7, 4.0 Hz), 3.58 (dq, 1H, J = 6.4, 6.0 Hz), 3.22 (s, 3H), 1.19 (d, 3H, J = 6.9 Hz), 1.17 (d, 3H, J = 6.9 Hz), 1.03 (d, 3H, J = 6.0 Hz).
339			^{1}H-NMR (DMSO-d_6) δ: 8.21 (s, 1H), 7.42-7.39 (m, 2H), 7.20-7.16 (m, 2H), 4.85 (quint, 1H, J = 6.6 Hz), 4.71-4.65 (m, 1H), 4.41 (s, 2H), 3.58-3.53 (m, 3H), 3.48-3.44 (m, 1H), 3.24 (s, 3H), 1.09 (d, 6H, J = 6.6 Hz).
340		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.82 (br s, 1H), 8.72 (s, 1H), 7.44-7.41 (m, 2H), 7.21-7.17 (m, 2H), 4.77 (sep, 1H, J = 6.6 Hz), 4.65 (ddd, 1H, J = 8.2, 4.1, 0.9 Hz), 4.47 (s, 2H), 3.88 (dd, 1H, J = 14.0, 4.1 Hz), 3.76 (dd, 1H, J = 14.0, 0.9 Hz), 3.52 (dq, 1H, J = 8.2, 6.2 Hz), 3.03 (s, 3H), 1.21 (d, 3H, J = 6.2 Hz), 1.20 (d, 3H, J = 6.6 Hz), 1.17 (d, 3H, J = 6.6 Hz).
341		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.95 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.68 (dd, 1H, J = 13.8, 1.5 Hz), 4.47 (s, 2H), 4.35 (dd, 1H, J = 13.8, 3.9 Hz), 4.10 (quint, 1H, J = 6.6 Hz), 3.96 (ddd, 1H, J = 6.6, 3.9, 1.5 Hz), 3.41 (dq, 1H, J = 6.6, 6.4 Hz), 3.24 (s, 3H), 1.39 (d, 3H, J = 6.6 Hz), 1.34 (d, 3H, J = 6.6 Hz), 1.02 (d, 3H, J = 6.4 Hz).
342		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.72 (s, 1H), 7.45-7.41 (m, 3H), 7.22-7.17 (m, 2H), 4.77 (quint, 1H, J = 6.8 Hz), 4.60 (ddd, 1H, J = 8.4, 4.2, 0.9 Hz), 4.47 (s, 2H), 3.88 (dd, 1H, J = 14.3, 4.2 Hz), 3.74 (dd, 1H, J = 14.3, 0.9 Hz), 3.56 (dq, 1H, J = 8.4, 6.2 Hz), 3.41 (dq, 1H, J = 9.5, 7.1 Hz), 2.91 (dq, 1H, J = 9.5, 7.1 Hz), 1.22 (d, 3H, J = 6.2 Hz), 1.20 (d, 3H, J = 6.8 Hz), 1.17 (d, 3H, J = 6.8 Hz), 0.75 (t, 3H, J = 7.1 Hz).

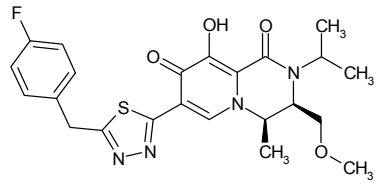
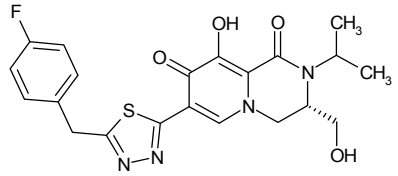
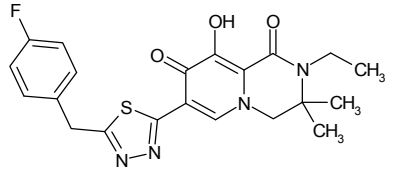
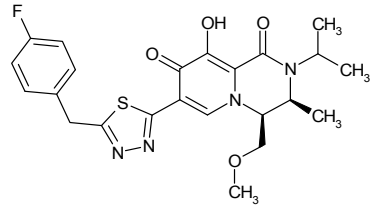
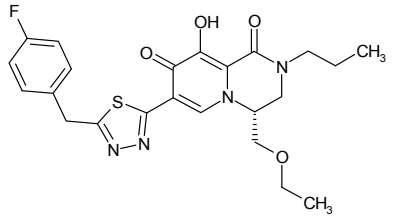
CUADRO 1-95

No.	fórmula estructural	sal	^{1}H- NMR
343		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.85 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.15 (m, 2H), 4.66 (dd, 1H, J = 12.4, 1.5 Hz), 4.48 (sep, 1H, J = 6.6 Hz), 4.47 (s, 2H), 4.35 (dd, 1H, J = 13.2, 3.7 Hz), 4.20-4.16 (m, 1H), 3.54 (dd, 1H, J = 10.5, 4.1 Hz), 3.45-3.30 (m, 3H), 1.30 (d, 3H, J = 6.6 Hz), 1.28 (d, 3H, J = 6.6 Hz), 0.96 (t, 3H, J = 6.9 Hz).
344			^{1}H-NMR (DMSO-d_6) δ: 12.81 (s, 1H), 8.80 (s, 1H), 7.44-7.39 (m, 2H), 7.22-7.16 (m, 2H), 4.99-4.95 (m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 3.84 (dd, 1H, J = 13.7, 3.9 Hz), 3.75 (dd, 1H, J = 13.9, 1.6 Hz), 3.63 (dd, 1H, J = 10.2, 6.0 Hz), 3.57 (dd, 1H, J = 10.2, 7.7 Hz), 3.25 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
345			^{1}H-NMR (DMSO-d_6) δ: 8.10 (s, 1H), 7.41-7.36 (m, 2H), 7.20-7.14 (m, 2H), 4.83 (quint, 1H, J = 6.7 Hz), 4.62-4.57 (m, 1H), 4.38 (s, 2H), 3.57-3.44 (m, 4H), 3.25 (s, 3H), 1.05 (d, 6H, J = 6.7 Hz).
346			^{1}H-NMR (DMSO-d_6) δ: 12.44 (br s, 1H), 8.85 (s, 1H), 7.44-7.37 (m, 2H), 7.23-7.14 (m, 2H), 4.70-4.61 (m, 1H), 4.54-4.41 (m, 1H), 4.47 (s, 2H), 4.39-4.30 (m, 1H), 4.25-4.14 (m, 1H), 3.53-3.34 (m, 2H), 3.21 (s, 3H), 1.30 (d, 3H, J = 6.3 Hz), 1.28 (d, 3H, J = 6.3 Hz).
347			^{1}H-NMR (DMSO-d_6) δ: 8.02 (br s, 1H), 7.42-7.33 (m, 2H), 7.21-7.13 (m, 2H), 4.73-4.59 (m, 1H), 4.38 (s, 2H), 4.34-4.22 (m, 1H), 4.07-3.96 (m, 1H), 3.89-3.78 (m, 1H), 3.30-3.05 (m, 2H), 3.24 (s, 3H), 1.13 (d, 3H, J = 7.0 Hz), 1.06 (d, 3H, J = 7.0 Hz).

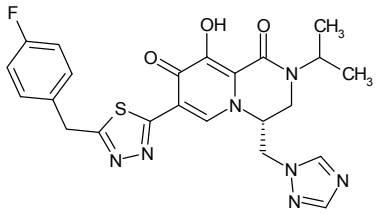
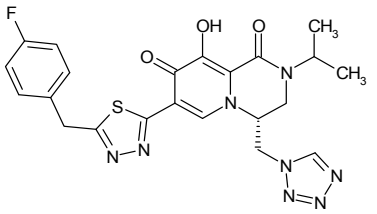
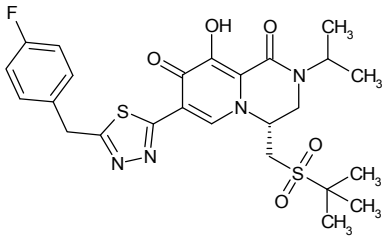
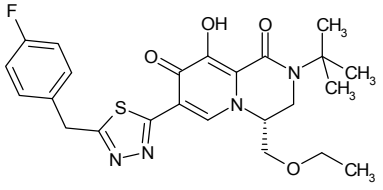
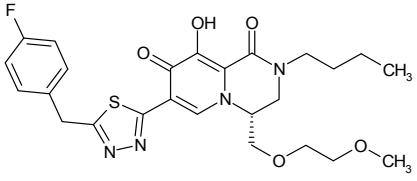
CUADRO 1-96

No.	fórmula estructural	sal	^{1}H- NMR
348		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.81 (br s, 1H), 8.72 (s, 1H), 7.47-7.37 (m, 2H), 7.23-7.14 (m, 2H), 4.83-4.71 (m, 1H), 4.69-4.60 (m, 1H), 4.47 (s, 2H), 3.88 (dd, 1H, J = 14.1, 3.7 Hz), 3.81-3.71 (m, 1H), 3.56-3.47 (m, 1H), 3.03 (s, 3H), 1.24-1.13 (m, 9H).
349		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.52 (s, 1H), 8.90 (s, 1H), 7.40 (dd, 2H, J = 8.3, 5.6 Hz), 7.17 (dd, 2H, J = 8.3, 8.4 Hz), 4.81 (d, 1H, J = 14.1 Hz), 4.46 (s, 2H), 4.38-4.27 (m, 2H), 3.98 (s, 1H), 3.62-3.56 (m, 1H), 3.04 (s, 3H), 1.33 (t, 6H, J = 6.0 Hz), 1.18 (d, 3H, J = 7.0 Hz).
350		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (s, 1H), 8.91 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.15 (m, 2H), 4.78 (quint, 1H, J = 6.9 Hz), 4.70 (dd, 1H, J = 6.4, 4.2 Hz), 4.47 (s, 2H), 3.86 (d, 1H, J = 13.7 Hz), 3.77 (dd, 1H, J = 13.7, 4.2 Hz), 3.58 (dq, 1H, J = 6.4, 6.0 Hz), 3.21 (s, 3H), 1.19 (d, 3H, J = 6.9 Hz), 1.17 (d, 3H, J = 6.9 Hz), 1.02 (d, 3H, J = 6.0 Hz).
351		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.71 (br s, 1H), 8.56 (s, 1H), 7.44-7.36 (m, 2H), 7.23-7.14 (m, 2H), 4.70-4.60 (m, 1H), 4.50-4.38 (m, 1H), 4.47 (s, 2H), 4.08-4.02 (m, 1H), 3.61 (dd, 1H, J = 11.1, 3.7 Hz), 3.53 (dd, 1H, J = 11.1, 3.9 Hz), 3.27 (q, 2H, J = 7.4 Hz), 1.75 (d, 3H, J = 6.5 Hz), 1.32 (t, 6H, J = 7.0 Hz), 0.82 (t, 3H, J = 7.0 Hz).
352			^{1}H-NMR (DMSO-d_6) δ: 12.79 (br s, 1H), 8.74 (s, 1H), 7.45-7.38 (m, 2H), 7.23-7.15 (m, 2H), 5.32-5.23 (m, 1H), 4.81-4.65 (m, 2H), 4.47 (s, 2H), 3.86-3.64 (m, 3H), 3.60-3.51 (m, 1H), 1.16 (d, 3H, J = 6.7 Hz), 1.15 (d, 3H, J = 6.7 Hz).

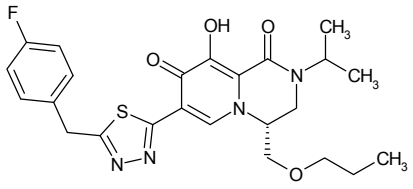
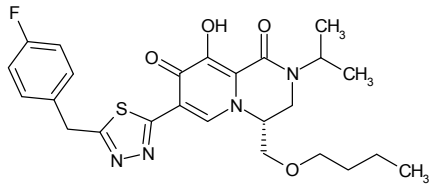
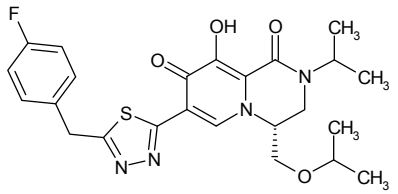
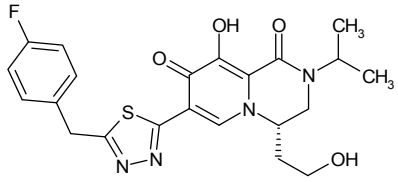
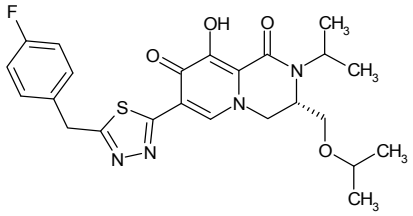
CUADRO 1-97

No.	fórmula estructural	sal	^{1}H- NMR
353		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (br s, 1H), 8.56 (s, 1H), 7.44-7.36 (m, 2H), 7.23-7.14 (m, 2H), 4.70-4.59 (m, 1H), 4.49-4.37 (m, 1H), 4.47 (s, 2H), 4.11-4.03 (m, 1H), 3.59-3.46 (m, 2H), 3.11 (s, 3H), 1.75 (d, 3H, J = 6.5 Hz), 1.32 (t, 6H, J = 6.5 Hz).
354		HBr	^{1}H-NMR (DMSO-D_6) δ: 8.80 (s, 1H), 7.43-7.37 (m, 2H), 7.21-7.14 (m, 2H), 4.70-4.64 (m, 1H), 4.55-4.44 (m, 3H), 4.33 (dd, 1H, J = 13.3, 3.6 Hz), 3.99-3.93 (m, 1H), 3.56 (dd, 1H, J = 11.4, 3.7 Hz), 3.35 (dd, 1H, J = 11.4, 8.1 Hz), 1.28 (d, 3H, J = 6.7 Hz), 1.27 (d, 3H, J = 6.7 Hz).
355		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.78 (br s, 1H), 8.76 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.14 (m, 2H), 4.47 (s, 2H), 4.34 (s, 2H), 3.55 (q, 2H, J = 7.1 Hz), 1.36 (s, 6H), 1.19 (t, 3H, J = 7.1 Hz).
356		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.76 (s, 1H), 8.77 (s, 1H), 7.42-7.36 (m, 2H), 7.21-7.14 (m, 2H), 4.71 (ddd, 1H, J = 8.0, 2.2, 2.0 Hz), 4.56 (quint, 1H, J = 6.9 Hz), 4.46 (s, 2H), 4.19-4.09 (m, 2H), 3.93 (dd, 1H, J = 11.7, 2.2 Hz), 3.45 (s, 3H), 1.29 (d, 3H, J=6.9 Hz), 1.27 (d, 3H, J=6.9 Hz), 1.04 (d, 3H, J = 6.5 Hz).
357		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.76 (s, 1H), 8.80 (s, 1H), 7.41 (tt, 2H, J = 8.7, 3.1 Hz), 7.18 (tt, 2H, J = 8.9, 2.5 Hz), 4.94-4.88 (m, 1H), 4.46 (s, 2H), 4.06 (dd, 1H, J = 13.8, 4.3 Hz), 3.73-3.67 (m, 2H), 3.64-3.52 (m, 2H), 3.49-3.27 (m, 3H), 1.63-1.53 (m, 2H), 1.01 (t, 3H, J = 7.0 Hz), 0.89 (t, 3H, J = 8.2 Hz).

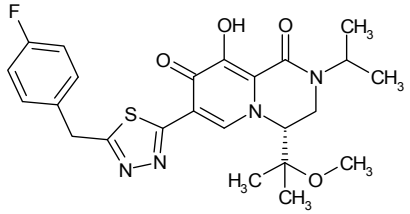
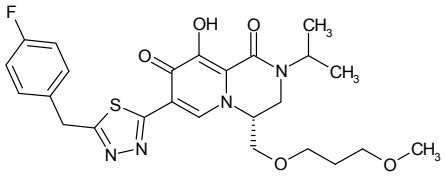
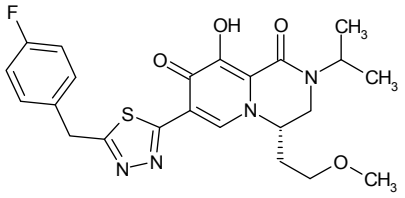
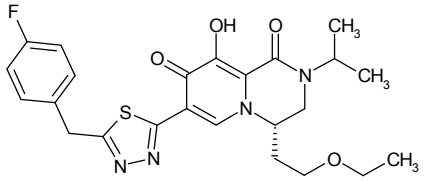
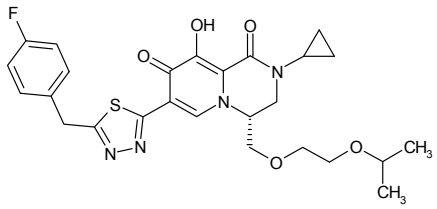
CUADRO 1-98

No.	fórmula estructural	sal	^{1}H- NMR
358		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.90 (br s, 1H), 8.37 (s, 1H), 8.07 (s, 1H), 8.00 (s, 1H), 7.45-7.37 (m, 2H), 7.23-7.13 (m, 2H), 5.28-5.18 (m, 1H), 4.89-4.60 (m, 3H), 4.44 (s, 2H), 3.98-3.83 (m, 2H), 1.25 (d, 3H, J = 6.7 Hz), 1.18 (d, 3H, J = 6.7 Hz).
359		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.88 (br s, 1H), 8.99 (s, 1H), 8.20 (s, 1H), 7.46-7.37 (m, 2H), 7.24-7.14 (m, 2H), 5.48-5.38 (m, 1H), 5.37-5.19 (m, 2H), 4.84-4.72 (m, 1H), 4.45 (s, 2H), 3.96 (d, 2H, J = 3.0 Hz), 1.25 (d, 3H, J = 6.7 Hz), 1.17 (d, 3H, J = 6.7 Hz).
360		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.85 (br s, 1H), 8.75 (s, 1H), 7.45-7.37 (m, 2H), 7.22-7.14 (m, 2H), 5.52-5.41 (m, 1H), 4.81-4.71 (m, 1H), 4.47 (s, 2H), 3.98-3.81 (m, 2H), 3.66 (d, 2H, J = 7.0 Hz), 1.29 (s, 9H), 1.21 (d, 3H, J = 6.5 Hz), 1.15 (d, 3H, J = 6.5 Hz).
361		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.94 (s, 1H), 8.80 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.15 (m, 2H), 4.89-4.85 (m, 1H), 4.47 (s, 2H), 3.96 (dd, 1H, J = 14.0, 1.5 Hz), 3.87 (dd, 1H, J = 14.0, 3.0 Hz), 3.70 (dd, 1H, J = 10.2, 6.7 Hz), 3.62 (dd, 1H, J = 10.2, 7.5 Hz), 3.50-3.41 (m, 2H), 1.49 (s, 9H), 1.05 (t, 3H, J = 6.9 Hz).
362		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.80 (s, 1H), 7.44-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.94-4.89 (m, 1H), 4.47 (s, 2H), 4.06 (dd, 1H, J = 13.6, 4.3 Hz), 3.77-3.72 (m, 2H), 3.70-3.46 (m, 5H), 3.38-3.31 (m, 3H), 3.11 (s, 3H), 1.60-1.52 (m, 2H), 1.37-1.27 (m, 2H), 0.92 (t, 3H, J = 7.4 Hz).

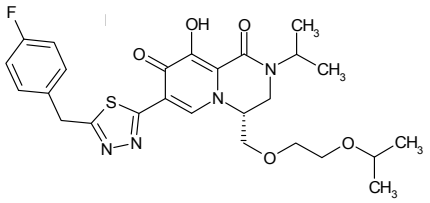
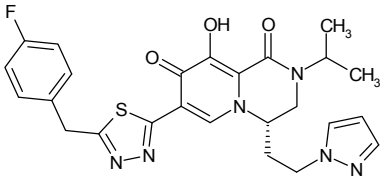
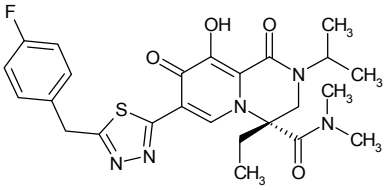
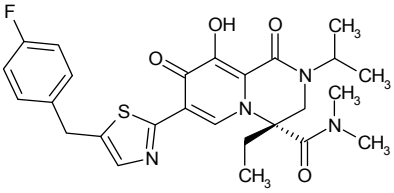
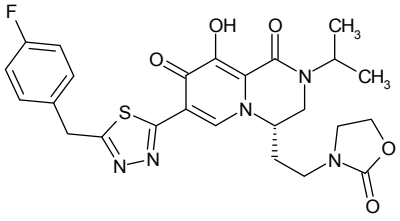
CUADRO 1-99

No.	fórmula estructural	sal	^{1}H- NMR
363		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.82 (s, 1H), 7.46-7.38 (m, 2H), 7.24-7.14 (m, 2H), 5.01-4.91 (br m, 1H), 4.77 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 3.88-3.54 (m, 4H), 3.41-3.24 (m, 2H), 1.41 (td, 2H, J = 13.9, 7.2 Hz), 1.17 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz), 0.74 (t, 3H, J = 7.2 Hz).
364		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.80 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.13 (m, 2H), 4.99-4.89 (m, 1H), 4.76 (sep, 1H, J = 7.0), 4.46 (s, 2H), 3.88-3.52 (m, 4H), 3.43-3.24 (m, 2H), 1.40-1.29 (m, 2H), 1.22-1.09 (m, 8H), 0.69 (t, 3H, J = 7.3 Hz).
365		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.84 (br s, 1H), 8.83 (s, 1H), 7.46-7.38 (m, 2H), 7.23-7.15 (m, 2H), 4.94-4.71 (m, 2H), 4.47 (s, 2H), 3.85-3.45 (m, 5H), 1.21-1.12 (m, 6H), 1.02 (d, 3H, J = 6.0 Hz), 0.96 (d, 3H, J = 6.3 Hz).
366			^{1}H-NMR (DMSO-d_6) δ: 12.77 (s, 1H), 8.80 (s, 1H), 7.45-7.38 (m, 2H), 7.23-7.14 (m, 2H), 4.91-4.83 (m, 1H), 4.83-4.73 (m, 2H), 4.47 (s, 2H), 3.86 (dd, 1H, J = 14.1, 3.5 Hz), 3.76-3.67 (m, 1H), 3.54-3.43 (m, 1H), 1.96-1.71 (m, 2H), 1.19 (d, 3H, J = 7.0 Hz), 1.16 (d, 3H, J = 6.7 Hz).
367		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.42 (br s, 1H), 8.84 (s, 1H), 7.45-7.37 (m, 2H), 7.23-7.14 (m, 2H), 4.69-4.63 (m, 1H), 4.53-4.44 (m, 3H), 4.35 (dd, 1H, J = 13.3, 4.0 Hz), 4.18-4.11 (m, 1H), 3.55 (dd, 1H, J = 10.5, 3.6 Hz), 3.48-3.39 (m, 2H), 1.30 (d, 3H, J = 6.9 Hz), 1.28 (d, 3H, J = 6.9 Hz), 0.95-0.90 (m, 6H).

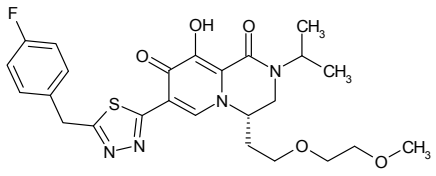
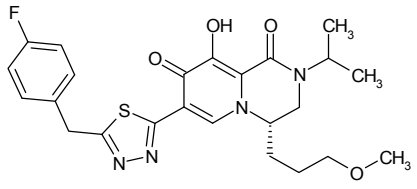
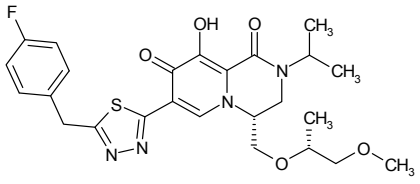
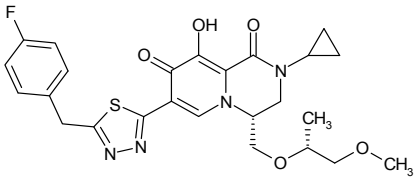
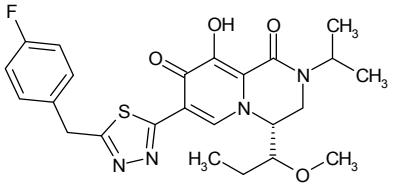
CUADRO 1-100

No.	fórmula estructural	sal	^{1}H- NMR
368		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.78 (s, 1H), 7.44-7.40 (m, 2H), 7.22-7.16 (m, 2H), 4.74-4.70 (m, 1H), 4.74 (quint, 1H, J = 7.1 Hz), 4.47 (s, 2H), 3.91-3.82 (m, 2H), 3.05 (s, 3H), 1.20 (d, 3H, J = 7.1 Hz), 1.19 (s, 3H), 1.18 (d, 3H, J = 7.1 Hz), 1.10 (s, 3H).
369		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (s, 1H), 8.81 (s, 1H), 7.44-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.95 (s, 1H), 4.80-4.73 (m, 1H), 4.47 (s, 2H), 3.85 (dd, 1H, J = 13.7, 4.0 Hz), 3.75 (d, 1H, J = 13.7 Hz), 3.67 (dd, 1H, J = 10.3, 5.4 Hz), 3.58 (dd, 1H, J = 10.3, 7.7 Hz), 3.45 (dt, 1H, J = 11.4, 4.6 Hz), 3.34 (dt, 1H, J = 11.4, 4.8 Hz), 3.20-3.13 (m, 2H), 3.00 (s, 3H), 1.64-1.58 (m, 2H), 1.16 (dd, 6H, J = 6.9, 2.4 Hz).
370		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.78 (br s, 1H), 8.72 (s, 1H), 7.46-7.38 (m, 2H), 7.24-7.15 (m, 2H), 4.91-4.81 (m, 1H), 4.84-4.72 (m, 1H), 4.47 (s, 2H), 3.89-3.65 (m, 2H), 3.45-3.35 (m, 1H), 3.20-3.07 (m, 1H), 3.18 (s, 3H), 2.07-1.93 (m, 1H), 1.93-1.80 (m, 1H), 1.18 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
371		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (br s, 1H), 8.75 (s, 1H), 7.47-7.37 (m, 2H), 7.24-7.15 (m, 2H), 4.91-4.73 (m, 2H), 4.47 (s, 2H), 3.90-3.63 (m, 2H), 3.58-3.01 (m, 4H), 2.11-1.79 (m, 2H), 1.19 (d, 3H, J = 7.2 Hz), 1.16 (d, 3H, J = 7.2 Hz), 1.03 (t, 3H, J = 7.2 Hz).
372		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.81 (br s, 1H), 8.80 (s, 1H), 7.44-7.36 (m, 2H), 7.23-7.14 (m, 2H), 4.93-4.84 (m, 1H), 4.47 (s, 2H), 4.04 (dd, 1H, J = 13.7, 4.0 Hz), 3.69 (dd, 1H, J = 10.5, 5.6 Hz), 3.66-3.59 (m, 2H), 3.53-3.32 (m, 5H), 2.93-2.85 (m, 1H), 0.96-0.69 (m, 4H), 0.93 (d, 3H, J = 6.0 Hz), 0.90 (d, 3H, J = 6.0 Hz).

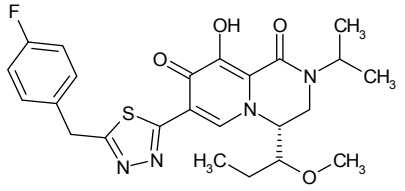
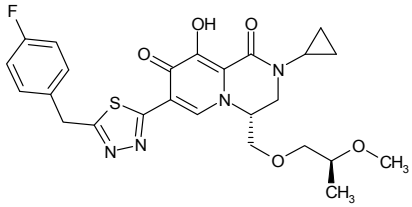
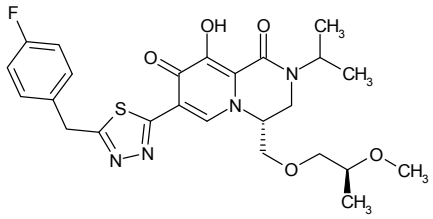
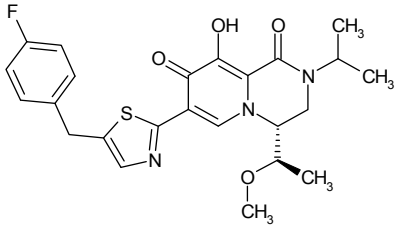
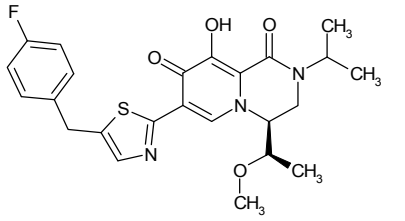
CUADRO 1-101

No.	fórmula estructural	sal	^{1}H- NMR
373		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.80 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 5.00-4.91 (m, 1H), 4.77 (sep, 1H, J = 6.9 Hz), 4.47 (s, 2H), 3.84 (dd, 1H, J = 13.7, 4.0 Hz), 3.80-3.74 (m, 1H), 3.71 (dd, 1H, J = 10.3, 5.8 Hz), 3.65 (dd, 1H, J = 10.3, 7.9 Hz), 3.54-3.32 (m, 5H), 1.17 (d, 3H, J = 6.9 Hz), 1.16 (d, 3H, J = 6.9 Hz), 0.92 (d, 3H, J = 6.0 Hz), 0.89 (d, 3H, J = 6.0 Hz).
374		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.89 (s, 1H), 7.70 (d, 1H, J = 2.2 Hz), 7.45 (d, 1H, J = 1.8 Hz), 7.44-7.39 (m, 2H), 7.22-7.16 (m, 2H), 6.20 (dd, 1H, J = 2.2, 1.8 Hz), 4.86-4.82 (m, 1H), 4.78 (quint, 1H, J = 7.1 Hz), 4.47 (s, 2H), 4.26-4.14 (m, 2H), 3.84 (dd, 1H, J = 13.6, 3.6 Hz), 3.68 (dd, 1H, J = 13.6, 0.9 Hz), 2.27-2.20 (m, 2H), 1.18 (d, 3H, J = 7.1 Hz), 1.14 (d, 3H, J = 7.1 Hz).
375		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.19 (br s, 1H), 8.41 (s, 1H), 7.46-7.38 (m, 2H), 7.23-7.14 (m, 2H), 4.80-4.68 (m, 1H), 4.47 (s, 2H), 4.08 (d, 1H, J = 14.1 Hz), 3.81 (d, 1H, J = 14.1 Hz), 2.93 (s, 6H), 2.61-2.11 (m, 2H), 1.19 (d, 3H, J = 7.0 Hz), 1.16 (d, 3H, J = 7.0 Hz), 0.91 (t, 3H, J = 7.2 Hz).
376		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.09 (br s, 1H), 8.30 (s, 1H), 7.70 (s, 1H), 7.38-7.28 (m, 2H), 7.19-7.10 (m, 2H), 4.80-4.69 (m, 1H), 4.20 (s, 2H), 4.06 (d, 1H, J = 14.1 Hz), 3.78 (d, 1H, J = 14.1 Hz), 2.91 (s, 6H), 2.47-2.07 (m, 2H), 1.22-1.12 (m, 6H), 0.87 (t, 3H, J = 7.2 Hz).
377		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.78 (br s, 1H), 8.96 (s, 1H), 7.43-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.87-4.80 (m, 1H), 4.80 (quint, 1H, J = 6.6 Hz), 4.47 (s, 2H), 4.23 (t, 2H, J = 7.9 Hz), 3.87-3.82 (m, 1H), 3.76-3.73 (m, 1H), 3.57-3.46 (m, 2H), 3.33-3.25 (m, 1H), 3.19-3.11 (m, 1H), 1.95 (dt, 2H, J = 7.1, 7.9 Hz), 1.22 (d, 3H, J = 6.6 Hz), 1.16 (d, 3H, J = 6.6 Hz).

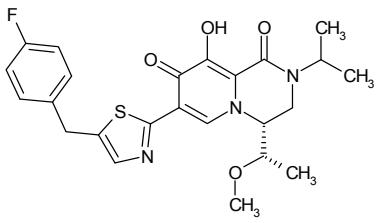
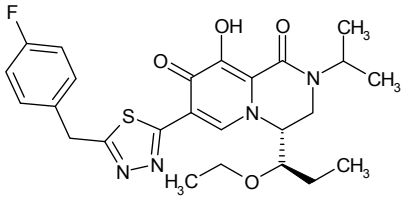
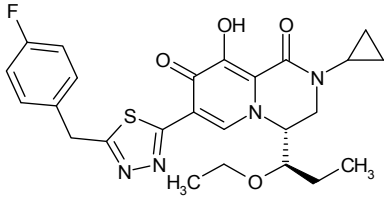
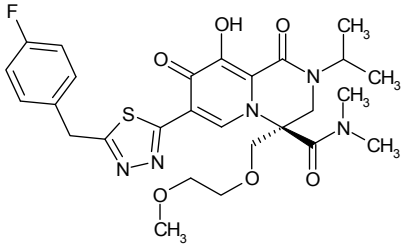
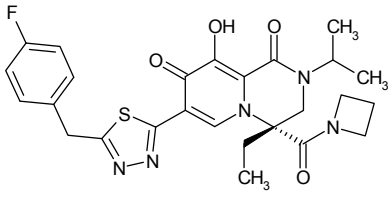
CUADRO 1-102

No.	fórmula estructural	sal	^{1}H- NMR
378		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.75 (br s, 1H), 8.75 (s, 1H), 7.44-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.88-4.83 (m, 1H), 4.78 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 3.85 (dd, 1H, J = 13.6, 3.6 Hz), 3.73 (dd, 1H, J = 13.6, 0.9 Hz), 3.53-3.48 (m, 1H), 3.45-3.31 (m, 4H), 3.29-3.18 (m, 1H), 3.15 (s, 3H), 2.04-1.96 (m, 1H), 1.91-1.83 (m, 1H), 1.19 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
379		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.78 (br s, 1H), 8.91 (s, 1H), 7.44-7.39 (m, 2H), 7.22-7.16 (m, 2H), 4.83-4.81 (m, 1H), 4.79 (sep, 1H, J = 6.7 Hz), 4.47 (s, 2H), 3.83 (dd, 1H, J = 13.8, 3.6 Hz), 3.72 (dd, 1H, J = 13.8, 1.5 Hz), 3.35-3.22 (m, 2H), 3.18 (s, 3H), 1.81-1.71 (m, 1H), 1.70-1.58 (m, 2H), 1.37-1.33 (m, 1H), 1.18 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 6.7 Hz).
380		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.85 (br s, 1H), 8.83 (s, 1H), 7.46-7.39 (m, 2H), 7.23-7.15 (m, 2H), 4.92-4.83 (br m, 1H), 4.81-4.70 (m, 1H), 4.47 (s, 2H), 3.85-3.62 (m, 4H), 3.59-3.48 (m, 1H), 3.26-3.18 (m, 2H), 3.17 (s, 3H), 1.21-1.12 (m, 6H), 0.91 (d, 3H, J = 6.5 Hz).
381		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.85 (br s, 1H), 8.83 (s, 1H), 7.45-7.37 (m, 2H), 7.23-7.15 (m, 2H), 4.86-4.76 (br m, 1H), 4.47 (s, 2H), 4.02 (dd, 1H, J = 13.4, 4.2 Hz), 3.77-3.58 (m, 3H), 3.57-3.48 (m, 1H), 3.26-3.19 (m, 2H), 3.18 (s, 3H), 2.93-2.84 (m, 1H), 0.92 (d, 3H, J = 6.3 Hz), 0.91-0.70 (m, 4H).
382		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (s, 1H), 8.71 (s, 1H), 7.44-7.42 (m, 2H), 7.21-7.17 (m, 2H), 4.78 (quint, 1H, J = 6.9 Hz), 4.70 (dd, 1H, J = 9.0, 3.7 Hz), 4.47 (s, 2H), 3.87 (dd, 1H, J = 14.5, 3.7 Hz), 3.74 (d, 1H, J = 14.5 Hz), 3.32 (ddd, 1H, J = 9.0, 3.6, 6.0 Hz), 2.96 (s, 3H), 1.79-1.70 (m, 1H), 1.54-1.43 (m, 1H), 1.19 (dd, 6H, J = 10.9, 6.9 Hz), 0.94 (t, 3H, J = 7.5 Hz).

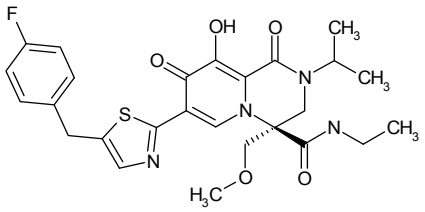
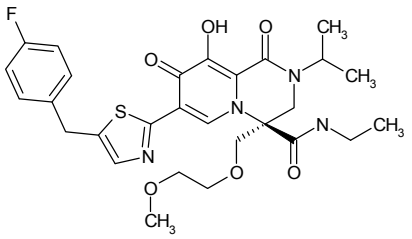
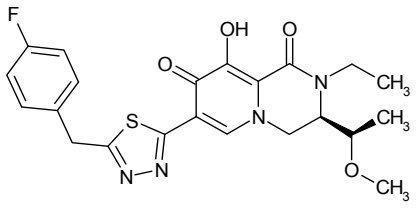
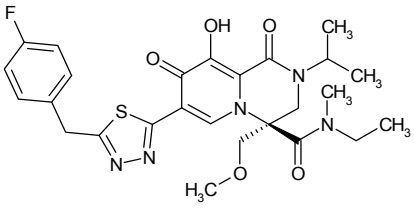
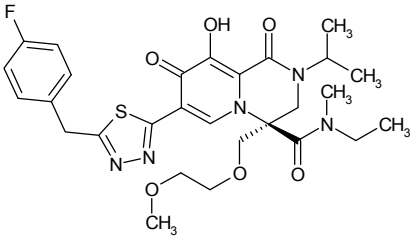
CUADRO 1-103

No.	fórmula estructural	sal	^{1}H- NMR
383		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.88 (s, 1H), 7.44-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.86-4.82 (m, 1H), 4.77 (quint, 1H, J = 6.9 Hz), 4.47 (s, 2H), 3.83-3.78 (m, 2H), 3.47-3.42 (m, 1H), 3.18 (s, 3H), 1.53-1.47 (m, 1H), 1.33-1.25 (m, 1H), 1.19 (d, 3H, J = 6.9 Hz), 1.17 (d, 3H, J = 6.9 Hz), 0.87 (t, 3H, J = 7.5 Hz).
384		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.82 (br s, 1H), 8.81 (s, 1H), 7.46-7.36 (m, 2H), 7.23-7.15 (m, 2H), 4.93-4.86 (m, 1H), 4.47 (s, 2H), 4.04 (dd, 1H, J = 13.2, 4.2 Hz), 3.75-3.57 (m, 3H), 3.39-3.25 (m, 3H), 3.10 (s, 3H), 2.92-2.87 (m, 1H), 0.93 (d, 3H, J = 5.8 Hz), 0.91-0.67 (m, 4H).
385		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.84 (br s, 1H), 8.82 (s, 1H), 7.45-7.38 (m, 2H), 7.23-7.15 (m, 2H), 5.00-4.92 (br m, 1H), 4.83-4.72 (m, 1H), 4.47 (s, 2H), 3.89-3.59 (m, 4H), 3.41-3.24 (m, 3H), 3.09 (s, 3H), 1.17 (d, 3H, J = 6.7 Hz), 1.15 (d, 3H, J = 6.7 Hz), 0.93 (d, 3H, J = 6.3 Hz).
386		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.69 (br s, 1H), 8.56 (s, 1H), 7.66 (s, 1H), 7.39-7.30 (m, 2H), 7.19-7.11 (m, 2H), 4.83-4.71 (m, 1H), 4.63-4.54 (m, 1H), 4.20 (s, 2H), 3.86 (dd, 1H, J = 14.1, 4.2 Hz), 3.78-3.70 (m, 1H), 3.55-3.45 (m, 1H), 3.02 (s, 3H), 1.23-1.14 (m, 9H).
387		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.68 (br s, 1H), 8.74 (s, 1H), 7.68 (s, 1H), 7.37-7.30 (m, 2H), 7.19-7.11 (m, 2H), 4.84-4.73 (m, 1H), 4.69-4.63 (m, 1H), 4.20 (s, 2H), 3.89-3.81 (m, 1H), 3.76 (dd, 1H, J = 13.7, 4.0 Hz), 3.60-3.52 (m, 1H), 3.22 (s, 3H), 1.21-1.15 (m, 6H), 1.00 (d, 3H, J = 6.0 Hz).

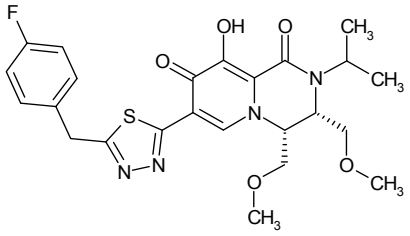
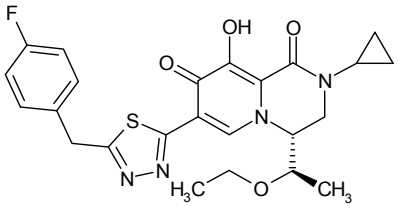
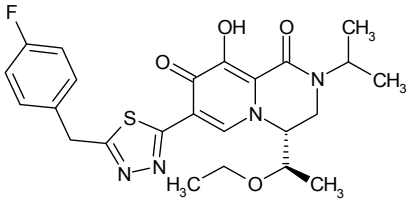
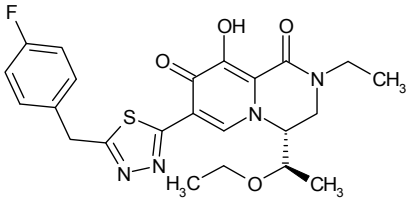
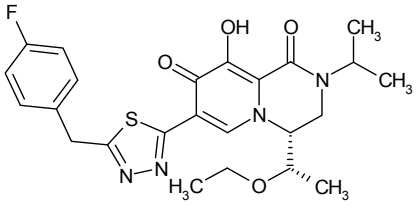
CUADRO 1-104

No.	fórmula estructural	sal	^{1}H- NMR
388		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.74 (s, 1H), 7.68 (s, 1H), 7.37-7.31 (m, 2H), 7.18-7.11 (m, 2H), 4.84-4.73 (m, 1H), 4.69-4.63 (m, 1H), 4.20 (s, 2H), 3.89-3.81 (m, 1H), 3.76 (dd, 1H, J = 13.7, 4.0 Hz), 3.60-3.51 (m, 1H), 3.22 (s, 3H), 1.21-1.14 (m, 6H), 1.00 (d, 3H, J = 6.0 Hz).
389		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.81 (s, 1H), 8.73 (s, 1H), 7.45-7.42 (m, 2H), 7.21-7.18 (m, 2H), 4.82-4.75 (m, 1H), 4.65 (dd, 1H, J = 9.1, 2.6 Hz), 4.47 (s, 3H), 3.87 (dd, 1H, J = 13.3, 3.8 Hz), 3.74 (d, 1H, J = 13.3 Hz), 3.39-3.27 (m, 2H), 2.77-2.73 (m, 1H), 1.79-1.70 (m, 1H), 1.51-1.43 (m, 1H), 1.20 (d, 3H, J = 6.9 Hz), 1.17 (d, 3H, J = 6.9 Hz), 0.96 (t, 3H, J = 7.5 Hz), 0.74 (t, 3H, J = 6.9 Hz).
390		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.72 (s, 1H), 7.44-7.42 (m, 2H), 7.21-7.17 (m, 2H), 4.62 (d, 1H, J = 5.6 Hz), 4.47 (s, 2H), 4.05 (dd, 1H, J = 13.9, 3.8 Hz), 3.57 (d, 1H, J = 13.3 Hz), 3.47-3.45 (m, 1H), 3.34 (dd, 1H, J = 9.3, 6.9 Hz), 2.94 (dd, 1H, J = 7.7, 3.6 Hz), 2.86 (dd, 1H, J = 9.3, 7.3 Hz), 1.55-1.38 (m, 2H), 0.94 (t, 3H, J = 7.0 Hz), 0.78 (t, 3H, J = 6.5 Hz), 0.42-0.36 (m, 1H), 0.34-0.27 (m, 2H), 0.24-0.20 (m, 1H).
391		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.90 (s, 1H), 8.86 (s, 1H), 7.47-7.37 (m, 2H), 7.23-7.15 (m, 2H), 4.81-4.65 (m, 1H), 4.47 (s, 2H), 4.41 (d, 1H, J = 12.1 Hz), 4.25 (d, 1H, J = 12.1 Hz), 4.06 (d, 1H, J = 14.1 Hz), 3.81 (d, 1H, J = 14.1 Hz), 3.75-3.63 (m, 2H), 3.62-3.36 (m, 2H), 3.21 (s, 3H), 3.11-2.73 (m, 6H), 1.16 (d, 3H, J = 6.8 Hz), 1.10 (d, 3H, J = 6.8 Hz).
392		HCl	^{1}H-NMR (DMSO-d_6) δ: 13.04 (s, 1H), 8.69 (s, 1H), 7.46-7.38 (m, 2H), 7.23-7.14 (m, 2H), 4.76-4.62 (m, 1H), 4.48 (s, 2H), 4.18-4.04 (m, 1H), 3.98 (d, 1H, J = 13.5 Hz), 3.94-3.82 (m, 2H), 3.78 (d, 1H, J = 13.5 Hz), 3.70-3.57 (m, 1H), 2.50-2.22 (m, 2H), 2.15-2.00 (m, 2H), 1.16 (t, 6H, J = 6.8 Hz), 1.03 (t, 3H, J = 7.5 Hz).

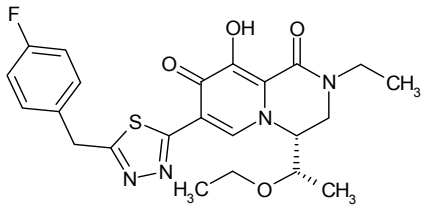
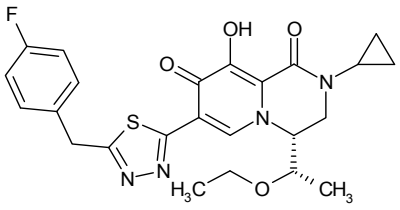
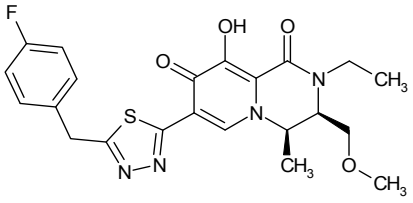
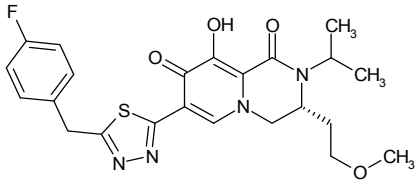
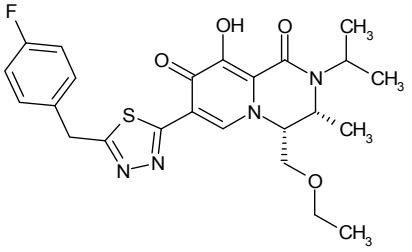
CUADRO 1-105

No.	fórmula estructural	sal	^{1}H- NMR
393		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.80 (s, 1H), 8.16 (t, 1H, J = 5.5 Hz), 7.67 (s, 1H), 7.38-7.28 (m, 2H), 7.19-7.10 (m, 2H), 4.76-4.63 (m, 1H), 4.20 (s, 2H), 4.17 (d, 1H, J = 11.9 Hz), 4.12 (d, 1H, J = 11.9 Hz), 4.03 (d, 1H, J = 13.9 Hz), 3.76 (d, 1H, J = 13.9 Hz), 3.40 (s, 3H), 3.21-2.92 (m, 2H), 1.13 (d, 3H, J = 6.8 Hz), 1.10 (d, 3H, J = 6.8 Hz), 0.99 (t, 3H, J = 7.5 Hz).
394		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.88 (s, 1H), 8.17 (t, 1H, J = 5.1 Hz), 7.66 (s, 1H), 7.37-7.29 (m, 2H), 7.19-7.10 (m, 2H), 4.76-4.64 (m, 1H), 4.33-4.16 (m, 2H), 4.20 (s, 2H), 4.04 (d, 1H, J = 13.9 Hz), 3.78 (d, 1H, J = 13.9 Hz), 3.72-3.66 (m, 2H), 3.57-3.50 (m, 2H), 3.25 (s, 3H), 3.20-2.96 (m, 2H), 1.14 (d, 3H, J = 6.8 Hz), 1.10 (d, 3H, J = 6.8 Hz), 1.04 (t, 3H, J = 7.3 Hz).
395		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.50 (br s, 1H), 8.95 (s, 1H), 7.44-7.36 (m, 2H), 7.22-7.15 (m, 2H), 4.69 (dd, 1H, J = 14.0, 1.5 Hz), 4.47 (s, 2H), 4.39 (dd, 1H, J = 14.0, 4.2 Hz), 4.04-3.98 (m, 1H), 3.97-3.92 (m, 1H), 3.51-3.43 (m, 1H), 3.26-3.18 (m, 1H), 3.18 (s, 3H), 1.19 (t, 3H, J = 7.2 Hz), 1.10 (d, 3H, J = 6.2 Hz).
396		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.92 (s, 1H), 8.77 (s, 1H), 7.47-7.37 (m, 2H), 7.23-7.14 (m, 2H), 4.79-4.66 (m, 1H), 4.47 (s, 2H), 4.28 (d, 1H, J = 11.9 Hz), 4.12 (d, 1H, J = 11.9 Hz), 4.06 (d, 1H, J = 14.3 Hz), 3.82 (d, 1H, J = 14.3 Hz), 3.47-3.29 (m, 5H), 3.05-2.78 (m, 3H), 1.16 (d, 3H, J = 7.1 Hz), 1.12 (d, 3H, J = 7.1 Hz), 1.08-0.97 (m, 3H).
397		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.93 (s, 1H), 8.85 (s, 1H), 7.48-7.34 (m, 2H), 7.24-7.13 (m, 2H), 4.77-4.65 (m, 1H), 4.47 (s, 2H), 4.38 (d, 1H, J = 11.9 Hz), 4.23 (d, 1H, J = 11.9 Hz), 4.06 (d, 1H, J = 14.3 Hz), 3.82 (d, 1H, J = 14.3 Hz), 3.73-3.24 (m, 6H), 3.19 (s, 3H), 3.06-2.84 (m, 3H), 1.16 (d, 3H, J = 6.6 Hz), 1.12 (d, 3H, J = 6.6 Hz), 1.07-0.94 (m, 3H).

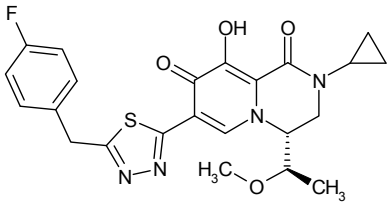
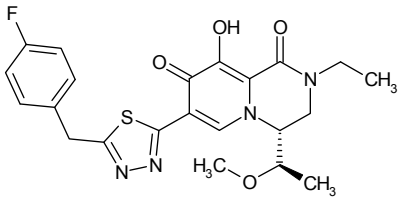
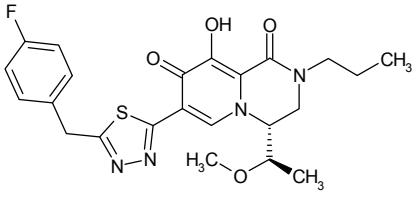
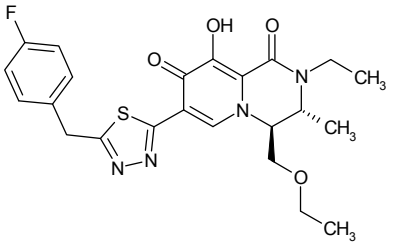
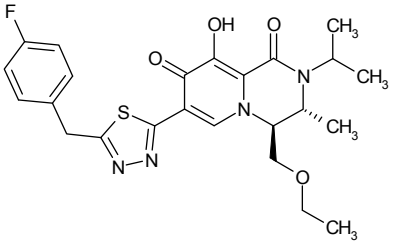
CUADRO 1-106

No.	fórmula estructural	sal	^{1}H- NMR
398		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.69 (br s, 1H), 8.78 (s, 1H), 7.44-7.36 (m, 2H), 7.22-7.14 (m, 2H), 4.84-4.79 (m, 1H), 4.47 (s, 2H), 4.46-4.37 (m, 1H), 4.22-4.13 (m, 2H), 4.01 (dd, 1H, J = 11.9, 2.2 Hz), 3.49-3.39 (m, 2H), 3.46 (s, 3H), 3.14 (s, 3H), 1.33 (d, 3H, J = 6.9 Hz), 1.30 (d, 3H, J = 6.9 Hz).
399		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.75 (s, 1H), 8.73 (s, 1H), 7.47-7.39 (m, 2H), 7.23-7.15 (m, 2H), 4.60-4.52 (m, 1H), 4.47 (s, 2H), 4.06 (dd, 1H, J = 14.1, 4.0 Hz), 3.65-3.55 (m, 2H), 3.47-3.36 (m, 1H), 3.02-2.88 (m, 2H), 1.16 (d, 3H, J = 6.2 Hz), 0.94-0.82 (m, 3H), 0.79 (t, 3H, J = 7.3 Hz), 0.75-0.64 (m, 1H).
400		HCl	^{1}H-NMR (DMSO-d_6) δ : 12.83 (s, 1H), 8.72 (s, 1H), 7.47-7.39 (m, 2H), 7.24-7.15 (m, 2H), 4.84-4.71 (m, 1H), 4.60 (dd, 1H, J = 8.6, 2.6 Hz), 4.47 (s, 2H), 3.88 (dd, 1H, J = 14.3, 4.0 Hz), 3.75 (d, 1H, J = 13.9 Hz), 3.58-3.53 (m, 1H), 3.46-3.34 (m, 1H), 2.97-2.85 (m, 1H), 1.26-1.14 (m, 9H), 0.75 (t, 3H, J = 6.9 Hz).
401		HCl	^{1}H-NMR (DMSO-d_6) δ : 8.72 (s, 1H), 7.47-7.39 (m, 2H), 7.24-7.15 (m, 2H), 4.60-4.53 (m, 1H), 4.47 (s, 2H), 4.11 (dd, 1H, J = 14.1, 4.2 Hz), 3.75 (d, 1H, J = 13.5 Hz), 3.65-3.37 (m, 4H), 3.00-2.90 (m, 1H), 1.22 (d, 3H, J = 6.2 Hz), 1.16 (t, 3H, J = 7.1 Hz), 0.77 (t, 3H, J = 6.9 Hz).
402		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.90 (s, 1H), 8.32 (s, 1H), 7.44-7.40 (m, 2H), 7.22-7.17 (m, 2H), 4.81-4.74 (m, 1H), 4.71 (t, 1H, J = 4.8 Hz), 4.47 (s, 2H), 3.87 (d, 1H, J = 12.5 Hz), 3.78 (dd, 1H, J = 13.9, 4.2 Hz), 3.71-3.65 (m, 1H), 3.57-3.50 (m, 1H), 3.17-3.10 (m, 1H), 1.19 (t, 6H, J = 7.0 Hz), 1.06 (d, 3H, J = 6.0 Hz), 1.02 (t, 3H, J = 6.9 Hz).

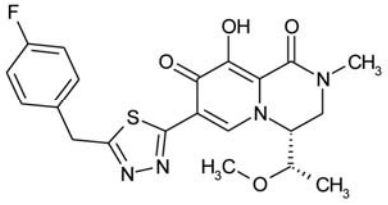
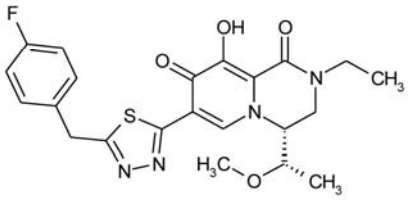
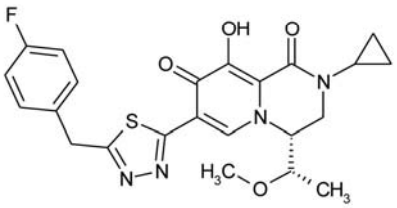
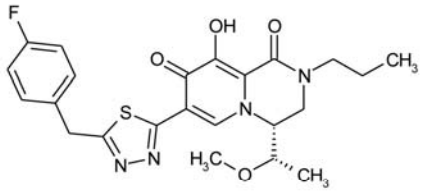
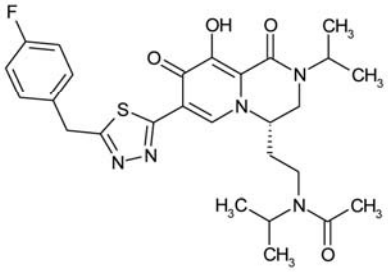
CUADRO 1-107

No.	fórmula estructural	sal	^{1}H- NMR
403		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (s, 1H), 8.91 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.69 (t, 1H, J = 4.6 Hz), 4.47 (s, 2H), 4.02 (dd, 1H, J = 14.1, 4.4 Hz), 3.84 (d, 1H, J = 13.7 Hz), 3.73-3.67 (m, 1H), 3.65-3.58 (m, 1H), 3.56-3.39 (m, 2H), 3.21-3.15 (m, 1H), 1.16 (t, 3H, J = 7.1 Hz), 1.07 (d, 3H, J = 6.0 Hz), 1.01 (t, 3H, J = 6.9 Hz).
404		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (s, 1H), 8.90 (s, 1H), 7.43-7.39 (m, 2H), 7.22-7.16 (m, 2H), 4.66 (t, 1H, J = 4.4 Hz), 4.47 (s, 2H), 3.98 (dd, 1H, J = 13.9, 4.2 Hz), 3.74-3.65 (m, 2H), 3.56-3.48 (m, 1H), 3.20-3.14 (m, 1H), 2.92-2.87 (m, 1H), 1.04 (d, 3H, J = 7.0 Hz), 1.02 (t, 3H, J = 7.2 Hz), 0.94-0.89 (m, 1H), 0.87-0.80 (m, 2H), 0.75-0.70 (m, 1H).
405		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (br s, 1H), 8.62 (s, 1H), 7.42-7.38 (m, 2H), 7.20-7.16 (m, 2H), 4.77-4.71 (m, 1H), 4.47 (s, 2H), 4.14 (q, 1H, J=4.0 Hz), 3.92-3.84 (m, 1H), 3.59 (d, 2H, J=4.4 Hz), 3.33-3.26 (m, 1H), 3.18 (s, 3H), 1.64 (d, 3H, J=6.5 Hz), 1.21 (t, 3H, J=7.1 Hz).
406		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.44 (br s, 1H), 8.89 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.66-4.60 (m, 1H), 4.56-4.45 (m, 3H), 4.34-4.27 (m, 1H), 4.10-4.04 (m, 1H), 3.50-3.36 (m, 2H), 3.24 (s, 3H), 1.89-1.79 (m, 1H), 1.73-1.62 (m, 1H), 1.28 (d, 6H, J = 6.9 Hz).
407		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (br s, 1H), 8.88 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.15 (m, 2H), 4.71-4.66 (m, 1H), 4.62-4.52 (m, 1H), 4.47 (s, 2H), 4.21-4.07 (m, 2H), 3.99 (dd, 1H, J = 11.7, 2.0 Hz), 3.71-3.62 (m, 2H), 1.32-1.22 (m, 9H), 1.05 (d, 3H, J = 6.4 Hz).

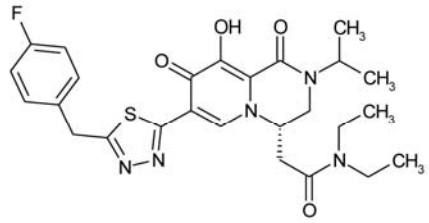
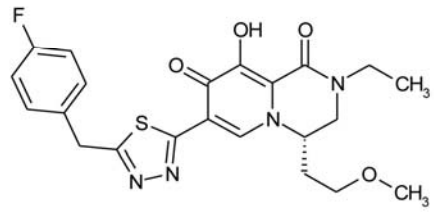
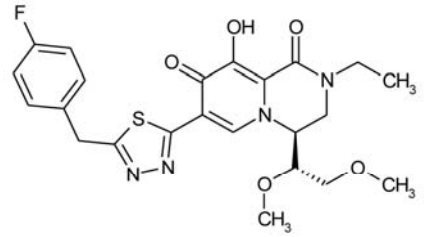
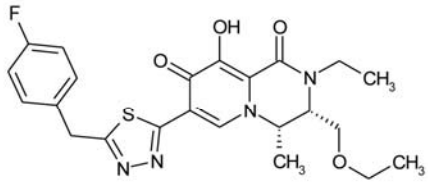
CUADRO 1-108

No.	fórmula estructural	sal	^{1}H- NMR
408		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.73 (s, 1H), 8.72 (s, 1H), 7.44-7.40 (m, 2H), 7.22-7.16 (m, 2H), 4.64-4.55 (m, 1H), 4.47 (s, 2H), 4.06 (dd, 1H, J = 14.1, 4.2 Hz), 3.66-3.49 (m, 2H), 3.06 (s, 3H), 2.96-2.86 (m, 1H), 1.15 (d, 3H, J = 6.0 Hz), 0.96-0.78 (m, 3H), 0.75-0.63 (m, 1H).
409		HCl	^{1}H-NMR (DMSO-D_6) δ: 12.73 (br s, 1H), 8.71 (s, 1H), 7.47-7.39 (m, 2H), 7.24-7.15 (m, 2H), 4.66-4.56 (m, 1H), 4.47 (s, 2H), 4.11 (dd, 1H, J = 14.1, 4.2 Hz), 3.76 (d, 1H, J = 13.7 Hz), 3.66-3.42 (m, 3H), 3.06 (s, 3H), 1.21 (d, 3H, J = 5.7 Hz), 1.16 (t, 3H, J = 7.3 Hz).
410		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.71 (br s, 1H), 8.71 (s, 1H), 7.47-7.39 (m, 2H), 7.24-7.15 (m, 2H), 4.65-4.57 (m, 1H), 4.47 (s, 2H), 4.10 (dd, 1H, J = 14.1, 4.0 Hz), 3.77 (d, 1H, J = 14.8 Hz), 3.59-3.38 (m, 3H), 3.05 (s, 3H), 1.60 (dt, 2H, J = 7.4, 7.4 Hz), 1.21 (d, 3H, J = 6.2 Hz), 0.90 (t, 3H, J = 7.4 Hz).
411		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.67 (s, 1H), 8.83 (s, 1H), 7.45-7.37 (m, 2H), 7.23-7.14 (m, 2H), 4.81 (t, 1H, J = 6.3 Hz), 4.48 (s, 2H), 4.09-3.99 (m, 1H), 3.97-3.85 (m, 1H), 3.68 (dd, 1H, J = 10.6, 5.7 Hz), 3.55 (dd, 1H, J = 10.6, 7.6 Hz), 3.51-3.30 (m, 2H), 3.19-3.06 (m, 1H), 1.27 (d, 3H, J = 6.6 Hz), 1.17 (t, 3H, J = 6.8 Hz), 1.01 (t, 3H, J = 7.3 Hz).
412		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.68 (br s, 1H), 8.83 (s, 1H), 7.46-7.37 (m, 2H), 7.23-7.15 (m, 2H), 4.85-4.76 (m, 1H), 4.67-4.57 (m, 1H), 4.48 (s, 2H), 4.20-4.10 (m, 1H), 3.64 (dd, 1H, J = 10.5, 5.8 Hz), 3.56-3.32 (m, 3H), 1.31-1.18 (m, 9H), 1.02 (t, 3H, J = 7.1 Hz).

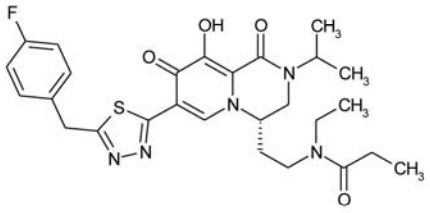
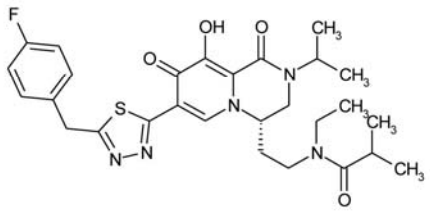
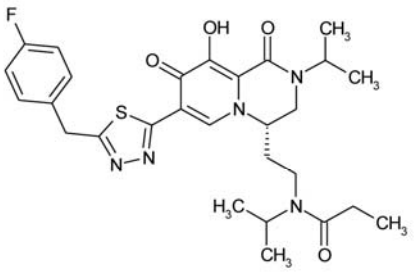
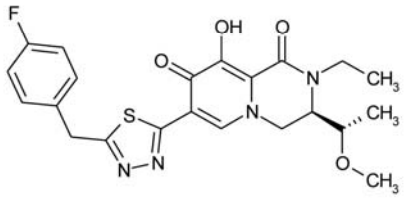
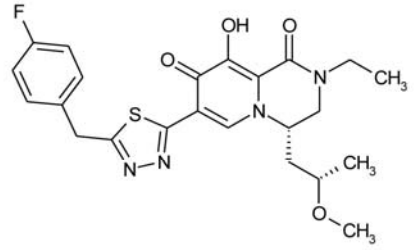
CUADRO 1-109

No.	fórmula estructural	sal	^{1}H-NMR
413		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.70 (s, 1H), 8.87 (s, 1H), 7.43-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.69 (t, 1H, J = 4.4 Hz), 4.47 (s, 2H), 4.09-4.04 (m, 1H), 3.76 (d, 1H, J = 12.9 Hz), 3.66-3.60 (m, 1H), 3.23 (s, 3H), 3.07 (s, 3H), 1.04 (d, 3H, J = 6.4 Hz).
414		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.76 (s, 1H), 8.90 (s, 1H), 7.44-7.39 (m, 2H), 7.21-7.17 (m, 2H), 4.69 (t, 1H, J = 4.4 Hz), 4.47 (s, 2H), 4.05-4.00 (m, 1H), 3.83 (d, 1H, J = 13.3 Hz), 3.67-3.59 (m, 2H), 3.45-3.39 (m, 1H), 3.23 (s, 3H), 1.16 (t, 3H, J = 7.1 Hz), 1.04 (d, 3H, J = 6.0 Hz).
415		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.75 (s, 1H), 8.89 (s, 1H), 7.43-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.66 (t, 1H, J = 4.6 Hz), 4.47 (s, 2H), 3.98 (dd, 1H, J = 13.7, 4.0 Hz), 3.71 (d, 1H, J = 12.5 Hz), 3.59-3.53 (m, 1H), 3.22 (s, 3H), 2.94-2.88 (m, 1H), 1.02 (d, 3H, J = 6.0 Hz), 0.95-0.89 (m, 1H), 0.85-0.80 (m, 2H), 0.75-0.69 (m, 1H).
416		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.75 (s, 1H), 8.90 (s, 1H), 7.43-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.69 (t, 1H, J = 4.8 Hz), 4.47 (s, 2H), 4.01 (dd, 1H, J = 13.9, 4.2 Hz), 3.83 (d, 1H, J = 12.9 Hz), 3.64-3.58 (m, 1H), 3.55-3.48 (m, 1H), 3.41-3.34 (m, 1H), 3.21 (s, 3H), 1.63-1.58 (m, 2H), 1.05 (d, 3H, J = 6.0 Hz), 0.91 (t, 3H, J = 7.3 Hz).
417		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.86 (s, 1H), 7.44-7.35 (m, 2H), 7.19-7.09 (m, 2H), 4.86-4.68 (m, 2H), 4.45 (s, 2H), 3.90-3.80 (m, 1H), 3.76-3.67 (m, 1H), 3.46-2.59 (m, 3H), 2.14-1.65 (m, 5H), 1.24 (d, 3H, J = 7.1 Hz), 1.19 (d, 3H, J = 7.1 Hz), 1.14-0.98 (m, 6H).

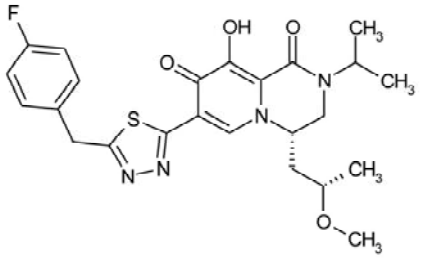
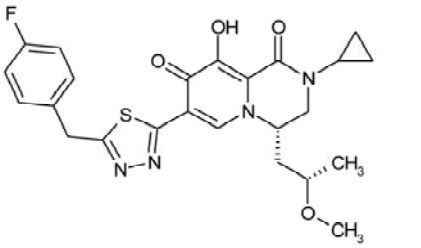
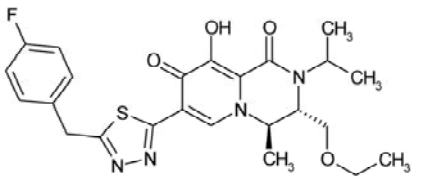
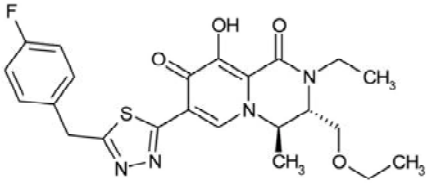
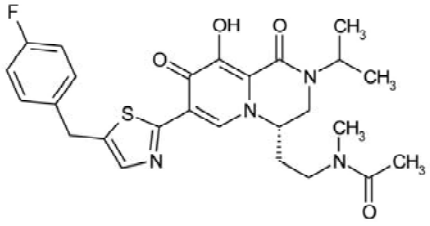
CUADRO 1-110

No.	fórmula estructural	sal	^{1}H -NMR
418		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.84 (s, 1H), 7.46-7.36 (m, 2H), 7.23-7.14 (m, 2H), 5.21-5.10 (m, 1H), 4.86-4.73 (m, 1H), 4.47 (s, 2H), 3.84 (d, 2H, J = 2.2 Hz), 3.37-3.11 (m, 4H), 2.87 (d, 2H, J = 7.1 Hz), 1.13 (t, 6H, J = 7.3 Hz), 0.99 (t, 3H, J = 7.1 Hz), 0.95 (t, 3H, J = 7.1 Hz).
419		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.73 (s, 1H), 7.47-7.38 (m, 2H), 7.23-7.15 (m, 2H), 4.89-4.76 (m, 1H), 4.47 (s, 2H), 4.20-3.99 (m, 2H), 3.72-3.57 (m, 2H), 3.51-3.32 (m, 2H), 3.18 (s, 3H), 2.15-1.83 (m, 2H), 1.16 (t, 3H, J = 7.3 Hz).
420		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.75 (br s, 1H), 8.64 (s, 1H), 7.46-7.39 (m, 2H), 7.22-7.15 (m, 2H), 4.77-4.71 (m, 1H), 4.47 (s, 2H), 4.11 (dd, 1H, J = 13.7, 4.0 Hz), 3.77-3.71 (m, 1H), 3.64-3.44 (m, 5H), 3.33 (s, 3H), 3.10 (s, 3H), 1.20-1.13 (m, 3H).
421		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (br s, 1H), 8.61 (s, 1H), 7.46-7.34 (m, 2H), 7.24-7.14 (m, 2H), 4.81-4.69 (m, 1H), 4.47 (s, 2H), 4.15-4.08 (m, 1H), 3.90 (td, 1H, J = 13.9, 7.0 Hz), 3.64 (d, 2H, J = 4.2 Hz), 3.38-3.21 (m, 3H), 1.65 (d, 3H, J = 7.0 Hz), 1.22 (t, 3H, J = 7.3 Hz), 0.89 (t, 3H, J = 6.8 Hz).
422		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.72 (br s, 1H), 8.55 (s, 1H), 7.45-7.36 (m, 2H), 7.23-7.14 (m, 2H), 4.72-4.61 (m, 1H), 4.49-4.38 (m, 1H), 4.47 (s, 2H), 4.09-4.02 (m, 1H), 3.61 (dd, 1H, J = 11.1, 3.0 Hz), 3.54 (dd, 1H, J = 11.1, 3.9 Hz), 3.27 (q, 2H, J = 7.0 Hz), 1.75 (d, 3H, J = 6.6 Hz), 1.32 (t, 6H, J = 6.8 Hz), 0.82 (t, 3H, J = 7.0 Hz).

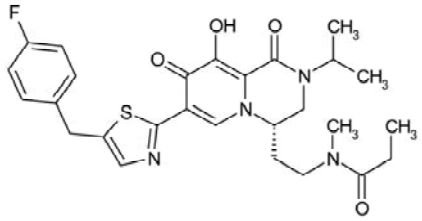
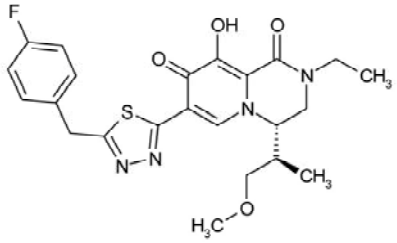
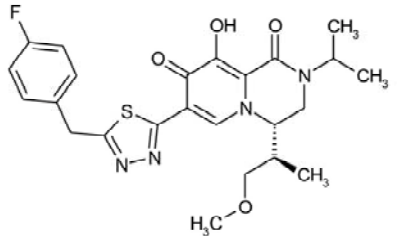
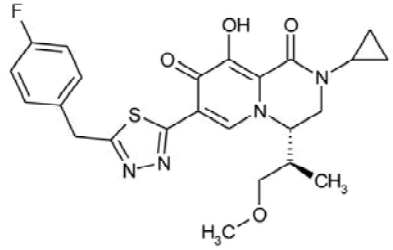
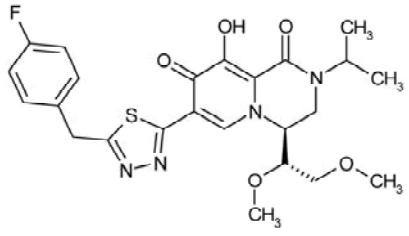
CUADRO 1-111

No.	fórmula estructural	sal	^{1}H -NMR
423		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.83 (s, 1H), 7.44-7.35 (m, 2H), 7.18-7.09 (m, 2H), 4.84-4.66 (m, 2H), 4.45 (s, 2H), 3.90-3.79 (m, 1H), 3.77-3.64 (m, 1H), 3.48-2.60 (m, 4H), 2.33-2.17 (m, 2H), 2.08-1.77 (m, 2H), 1.24 (d, 3H, J = 6.4 Hz), 1.19 (d, 3H, J = 6.6 Hz), 1.12-1.00 (m, 3H), 0.97 (t, 3H, J = 7.7 Hz).
424		HCl	^{1}H-NMR (DMSO-d_6) δ: 9.02 (s, 0.25H), 8.94 (s, 0.75H), 7.46-7.36 (m, 2H), 7.23-7.14 (m, 2H), 4.95-4.66 (br m, 2H), 4.47 (s, 2H), 3.92-3.67 (m, 2H), 3.53-2.98 (br m, 4H), 2.87-2.53 (br m, 1H), 2.14-1.63 (br m, 2H), 1.29-0.86 (br m, 15H).
425		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.86 (s, 1H), 7.44-7.35 (m, 2H), 7.19-7.08 (m, 2H), 4.85-4.69 (m, 2H), 4.45 (s, 2H), 4.22-3.98 (m, 2H), 3.90-3.80 (m, 1H), 3.78-3.68 (m, 1H), 3.13-3.00 (m, 1H), 2.35-2.15 (m, 2H), 2.09-1.93 (m, 1H), 1.87-1.71 (m, 1H), 1.24 (d, 3H, J = 6.6 Hz), 1.19 (d, 3H, J = 6.8 Hz), 1.07 (t, 6H, J = 6.4 Hz), 0.96 (t, 3H, J = 7.3 Hz).
426		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.49 (s, 1H), 8.91 (s, 1H), 7.42-7.39 (m, 2H), 7.20-7.16 (m, 2H), 4.80 (d, 1H, J = 13.3 Hz), 4.47 (s, 2H), 4.36 (dd, 1H, J = 13.7, 4.8 Hz), 3.96-3.89 (m, 2H), 3.65-3.60 (m, 1H), 3.28-3.20 (m, 1H), 3.08 (s, 3H), 1.21 (t, 3H, J = 7.1 Hz), 1.16 (d, 3H, J = 6.4 Hz).
427		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.65 (s, 1H), 7.44-7.39 (m, 2H), 7.22-7.16 (m, 2H), 4.88-4.84 (m, 1H), 4.46 (s, 2H), 4.08 (dd, 1H, J = 13.5, 3.8 Hz), 3.65-3.62 (m, 1H), 3.62 (dq, 1H, J = 13.7, 7.3 Hz), 3.45 (dq, 1H, J = 13.7, 7.3 Hz), 3.21 (s, 3H), 3.02-2.97 (m, 1H), 1.93-1.78 (m, 2H), 1.16 (t, 3H, J = 7.3 Hz), 1.04 (d, 3H, J = 6.0 Hz).

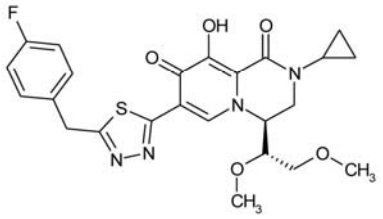
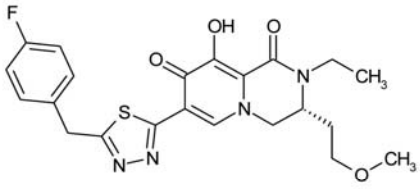
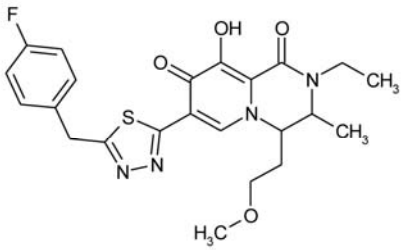
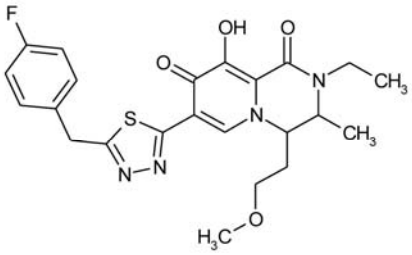
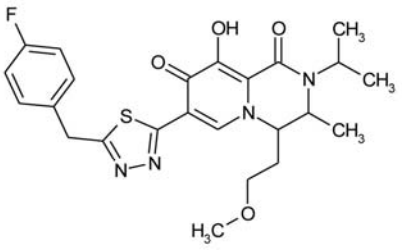
CUADRO 1-112

No.	fórmula estructural	sal	^{1}H-NMR
428		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (s, 1H), 8.64 (s, 1H), 7.44-7.40 (m, 2H), 7.21-7.17 (m, 2H), 4.91-4.87 (m, 1H), 4.78 (sep, 1H, J = 6.8 Hz), 4.46 (s, 2H), 3.84 (dd, 1H, J = 13.5, 3.6 Hz), 3.68 (dd, 1H, J = 13.5, 1.3 Hz), 3.22 (s, 3H), 2.99-2.95 (m, 1H), 1.86 (ddd, 1H, J = 14.6, 9.9, 3.1 Hz), 1.77 (ddd, 1H, J = 14.6, 10.4, 4.9 Hz), 1.18 (d, 3H, J = 6.8 Hz), 1.15 (d, 3H, J = 6.8 Hz), 1.04 (d, 3H, J = 6.0 Hz).
429		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (br s, 1H), 8.65 (s, 1H), 7.44-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.85-4.80 (m, 1H), 4.46 (s, 2H), 4.02 (dd, 1H, J = 13.2, 3.7 Hz), 3.54 (dd, 1H, J = 13.2, 0.9 Hz), 3.21 (s, 3H), 3.03-2.96 (m, 1H), 2.97-2.91 (m, 1H), 1.85-1.75 (m, 2H), 1.03 (d, 3H, J = 6.0 Hz), 0.95-0.72 (m, 4H).
430		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.48 (br s, 1H), 8.95 (s, 1H), 7.45-7.37 (m, 2H), 7.23-7.14 (m, 2H), 5.01-4.90 (m, 1H), 4.56 (sep, 1H, J = 6.8 Hz), 4.48 (s, 2H), 4.08-4.01 (m, 1H), 3.55 (dd, 1H, J = 10.5, 3.9 Hz), 3.45-3.31 (m, 3H), 1.40 (d, 3H, J = 6.6 Hz), 1.29 (d, 3H, J = 6.8 Hz), 1.28 (d, 3H, J = 6.8 Hz), 0.98 (t, 3H, J = 6.9 Hz).
431		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.50 (br s, 1H), 8.93 (s, 1H), 7.45-7.36 (m, 2H), 7.23-7.14 (m, 2H), 4.92 (q, 1H, J = 6.7 Hz), 4.48 (s, 2H), 4.04-3.96 (m, 2H), 3.59-3.47 (m, 2H), 3.44-3.31 (m, 2H), 3.22-3.09 (m, 1H), 1.42 (d, 3H, J = 6.7 Hz), 1.20 (t, 3H, J = 7.1 Hz), 0.97 (t, 3H, J = 6.9 Hz).
432		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.80-8.74 (m, 1H), 7.68 (s, 1H), 7.38-7.29 (m, 2H), 7.20-7.10 (m, 2H), 4.97-4.55 (m, 2H), 4.20 (s, 2H), 3.92-3.60 (m, 2H), 3.60-3.02 (m, 2H), 2.93 (s, 2H), 2.72 (s, 1H), 2.08-1.59 (m, 5H), 1.22 (d, 3H, J = 7.1 Hz), 1.16 (d, 3H, J = 6.4 Hz).

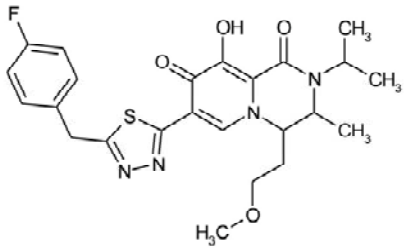
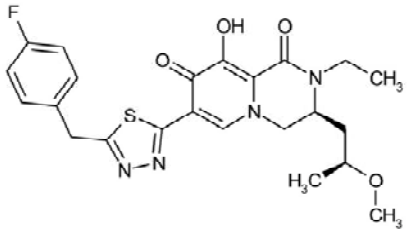
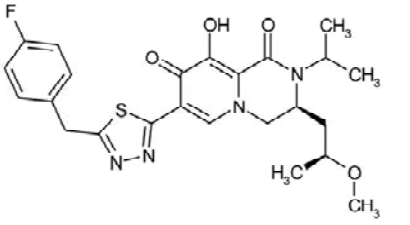
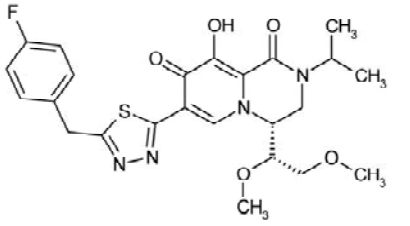
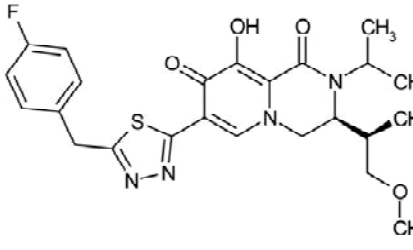
CUADRO 1-113

No.	fórmula estructural	sal	^{1}H-NMR
433		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.66 (s, 1H), 7.61 (s, 1H), 7.36-7.27 (m, 2H), 7.16-7.04 (m, 2H), 4.84-4.56 (m, 2H), 4.19 (s, 2H), 3.88-3.76 (m, 1H), 3.75-3.63 (m, 1H), 3.52-3.14 (m, 2H), 3.03-2.70 (m, 3H), 2.33-2.17 (m, 2H), 2.06-1.76 (m, 2H), 1.24 (d, 3H, J = 6.6 Hz), 1.19 (d, 3H, J = 6.6 Hz), 0.96 (t, 3H, J = 7.5 Hz).
434		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.63 (br s, 1H), 8.73 (s, 1H), 7.44-7.41 (m, 2H), 7.21-7.17 (m, 2H), 4.60-4.55 (m, 1H), 4.47 (s, 2H), 4.05 (dd, 1H, J = 13.9, 3.4 Hz), 3.78 (dd, 1H, J = 13.9, 1.1 Hz), 3.63 (dq, 1H, J = 13.5, 7.1 Hz), 3.48 (dq, 1H, J = 13.5, 7.1 Hz), 3.18 (dd, 1H, J = 9.9, 4.2 Hz), 3.02 (s, 3H), 2.88 (dd, 1H, J = 9.9, 3.4 Hz), 2.11-2.04 (m, 1H), 1.16 (t, 3H, J = 7.1 Hz), 1.07 (d, 3H, J = 6.8 Hz).
435		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.71 (br s, 1H), 8.75 (s, 1H), 7.44-7.41 (m, 2H), 7.22-7.17 (m, 2H), 4.79 (sep, 1H, J = 6.8 Hz), 4.60-4.57 (m, 1H), 4.46 (s, 2H), 3.82 (dd, 1H, J = 14.3, 3.5 Hz), 3.77 (dd, 1H, J = 14.3, 1.3 Hz), 3.16 (dd, 1H, J = 9.9, 4.1 Hz), 2.99 (s, 3H), 2.83 (dd, 1H, J = 9.9, 3.3 Hz), 2.06-2.02 (m, 1H), 1.20 (d, 3H, J = 6.8 Hz), 1.19 (d, 3H, J = 6.8 Hz), 1.08 (d, 3H, J = 6.8 Hz).
436		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.64 (br s, 1H), 8.73 (s, 1H), 7.44-7.40 (m, 2H), 7.21-7.17 (m, 2H), 4.57-4.54 (m, 1H), 4.46 (s, 2H), 4.01 (dd, 1H, J = 13.7, 3.6 Hz), 3.61 (dd, 1H, J = 13.7, 1.2 Hz), 3.17 (dd, 1H, J = 9.9, 4.4 Hz), 3.02 (s, 3H), 2.98-2.92 (m, 1H), 2.88 (dd, 1H, J = 9.9, 3.4 Hz), 2.07-1.99 (m, 1H), 1.03 (d, 3H, J = 6.9 Hz), 0.93-0.81 (m, 3H), 0.72-0.65 (m, 1H).
437		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.83 (br s, 1H), 8.65 (s, 1H), 7.46-7.40 (m, 2H), 7.22-7.16 (m, 2H), 4.83-4.71 (m, 2H), 4.47 (s, 2H), 3.93-3.86 (m, 1H), 3.79-3.73 (m, 1H), 3.60-3.47 (m, 3H), 3.33 (s, 3H), 3.08 (s, 3H), 1.22 (d, 3H, J = 6.9 Hz), 1.18 (d, 3H, J = 6.9 Hz).

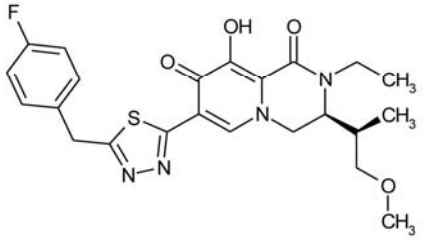
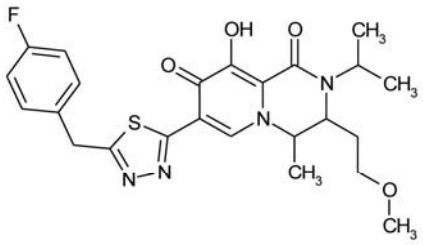
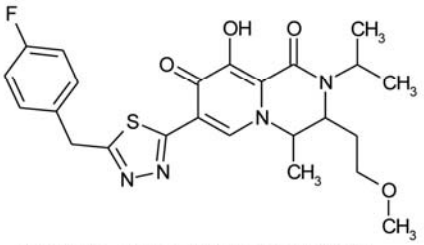
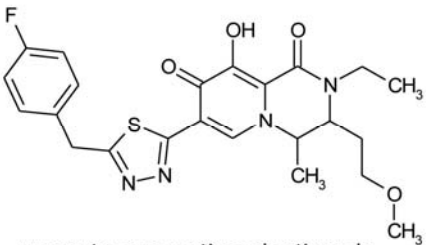
CUADRO 1-114

No.	fórmula estructural	sal	^{1}H-NMR
438		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.74 (br s, 1H), 8.64 (s, 1H), 7.46-7.39 (m, 2H), 7.22-7.15 (m, 2H), 4.76-4.70 (m, 1H), 4.47 (s, 2H), 4.10-4.02 (m, 1H), 3.67-3.60 (m, 1H), 3.60-3.53 (m, 1H), 3.48 (dd, 1H, J = 10.9, 4.0 Hz), 3.43 (dd, 1H, J = 10.9, 5.2 Hz), 3.32 (s, 3H), 3.10 (s, 3H), 2.96-2.88 (m, 1H), 0.95-0.73 (m, 4H).
439		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.46 (br s, 1H), 8.87 (s, 1H), 7.45-7.36 (m, 2H), 7.23-7.14 (m, 2H), 4.65-4.56 (m, 1H), 4.47 (s, 2H), 4.38 (dd, 1H, J = 13.7, 3.6 Hz), 4.07-3.98 (m, 1H), 3.91 (td, 1H, J = 13.9, 7.1 Hz), 3.48-3.33 (m, 2H), 3.23 (s, 3H), 3.11 (td, 1H, J = 13.9, 7.1 Hz), 1.91-1.79 (m, 1H), 1.79-1.67 (m, 1H), 1.20 (t, 3H, J = 7.1 Hz).
440	 racemato, que contiene dos tipos de diastereómeros del Ejemplo No. 441.	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.63 (s, 1H), 8.76 (s, 1H), 7.44-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.66 (dd, 1H, J = 9.7, 4.4 Hz), 4.47 (s, 2H), 3.97 (dd, 1H, J = 13.9, 6.2 Hz), 3.92-3.86 (m, 1H), 3.41-3.36 (m, 1H), 3.17-3.10 (m, 5H), 2.08-2.01 (m, 1H), 1.87-1.80 (m, 1H), 1.24 (d, 3H, J = 6.4 Hz), 1.19 (t, 3H, J = 7.1 Hz).
441	 racemato, que contiene dos tipos de diastereómeros del Ejemplo No. 440.	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.77 (s, 1H), 8.64 (s, 1H), 7.44-7.40 (m, 2H), 7.22-7.17 (m, 2H), 4.71-4.67 (m, 1H), 4.47 (s, 2H), 4.33-4.27 (m, 1H), 3.76 (td, 1H, J = 14.1, 7.1 Hz), 3.43-3.36 (m, 2H), 3.15 (s, 3H), 3.12-3.05 (m, 1H), 2.09-2.02 (m, 1H), 1.94-1.84 (m, 1H), 1.33 (d, 3H, J = 5.2 Hz), 1.14 (t, 3H, J = 7.1 Hz).
442	 racemato, que contiene dos tipos de diastereómeros del Ejemplo No. 443.	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.65 (s, 1H), 8.75 (s, 1H), 7.43-7.40 (m, 2H), 7.21-7.17 (m, 2H), 4.67-4.58 (m, 2H), 4.47 (s, 2H), 4.10-4.04 (m, 1H), 3.42-3.37 (m, 1H), 3.17 (s, 3H), 3.15-3.09 (m, 1H), 2.05-1.97 (m, 1H), 1.82-1.75 (m, 1H), 1.28-1.23 (m, 9H).

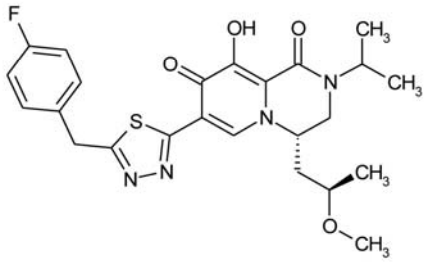
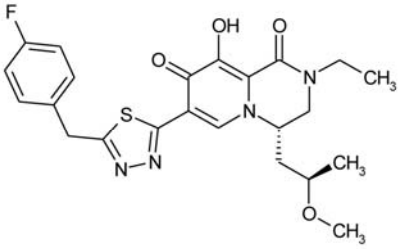
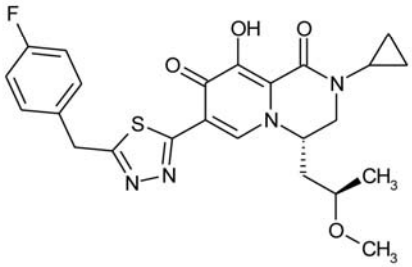
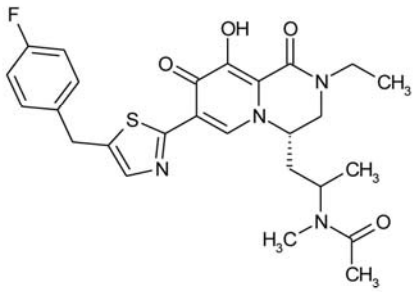
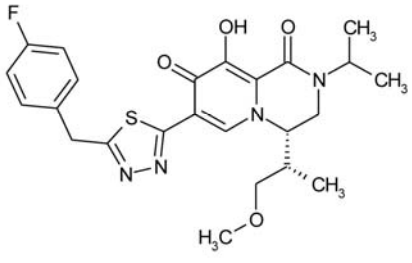
CUADRO 1-115

No.	fórmula estructural	sal	^{1}H -NMR
443	 racemato, que contiene dos tipos de diastereómeros del Ejemplo No. 442.	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.76 (s, 1H), 8.65 (s, 1H), 7.42-7.39 (m, 2H), 7.20-7.16 (m, 2H), 4.56-4.51 (m, 2H), 4.47 (s, 2H), 4.09-4.03 (m, 1H), 3.63-3.54 (m, 2H), 3.31 (s, 3H), 2.50-2.48 (m, 1H), 2.12-2.06 (m, 1H), 1.30 (d, 3H, J = 7.0 Hz), 1.28 (d, 3H, J = 7.0 Hz), 1.09 (d, 3H, J = 6.0 Hz).
444		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.48 (br s, 1H), 8.80 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.55 (dd, 1H, J = 13.2, 1.5 Hz), 4.47 (s, 2H), 4.38 (dd, 1H, J = 13.2, 3.5 Hz), 4.08-4.04 (m, 1H), 3.98 (dq, 1H, J = 13.5, 7.1 Hz), 3.42-3.37 (m, 1H), 3.20 (s, 3H), 3.06 (dq, 1H, J = 13.5, 7.1 Hz), 1.71-1.59 (m, 2H), 1.20 (t, 3H, J = 7.1 Hz), 1.06 (d, 3H, J = 6.2 Hz).
445		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.81 (s, 1H), 7.44-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.57 (dd, 1H, J = 13.2, 1.3 Hz), 4.47 (s, 2H), 4.45 (sep, 1H, J = 6.8 Hz), 4.31 (dd, 1H, J = 13.2, 3.3 Hz), 4.11-4.06 (m, 1H), 3.50-3.45 (m, 1H), 3.19 (s, 3H), 1.68-1.57 (m, 2H), 1.31 (d, 3H, J = 6.8 Hz), 1.28 (d, 3H, J = 6.8 Hz), 1.08 (d, 3H, J = 6.2 Hz).
446		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (br s, 1H), 8.75 (s, 1H), 7.45-7.39 (m, 2H), 7.22-7.16 (m, 2H), 4.86-4.75 (m, 2H), 4.47 (s, 2H), 3.86-3.80 (m, 1H), 3.76 (dd, 1H, J = 13.3, 3.6 Hz), 3.61 (dd, 1H, J = 11.7, 2.8 Hz), 3.58-3.51 (m, 1H), 3.30 (s, 3H), 3.18 (s, 3H), 2.97 (dd, 1H, J = 11.7, 2.8 Hz), 1.20 (d, 3H, J = 6.9 Hz), 1.17 (d, 3H, J = 6.9 Hz).
447		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.47 (br s, 1H), 8.99 (s, 1H), 7.44-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.73 (d, 1H, J = 13.7 Hz), 4.47 (s, 2H), 4.34 (dd, 1H, J = 13.7, 4.4 Hz), 4.23-4.14 (m, 1H), 4.05-4.00 (m, 1H), 3.46 (dd, 1H, J = 9.7, 8.1 Hz), 3.37 (dd, 1H, J = 9.7, 5.2 Hz), 3.30 (s, 3H), 2.22-2.11 (m, 1H), 1.38 (d, 3H, J = 6.9 Hz), 1.34 (d, 3H, J = 6.9 Hz), 0.60 (d, 3H, J = 7.3 Hz).

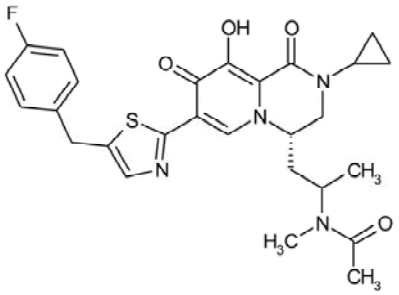
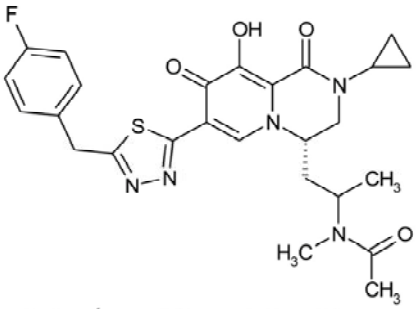
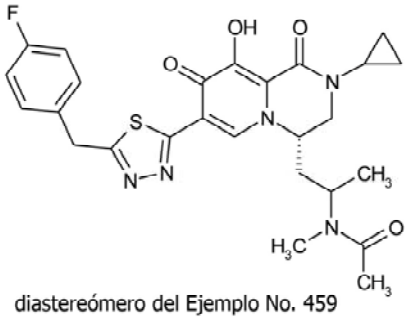
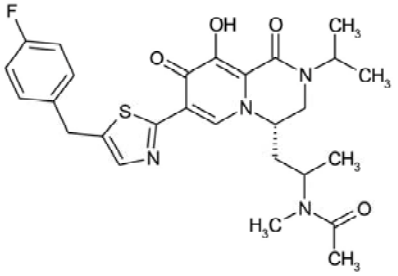
CUADRO 1-116

No.	fórmula estructural	sal	^{1}H-NMR
448		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.42 (br s, 1H), 9.00 (s, 1H), 7.44-7.37 (m, 2H), 7.22-7.14 (m, 2H), 4.76-4.68 (m, 1H), 4.47 (s, 2H), 4.37 (dd, 1H, J = 14.1, 4.0 Hz), 4.07-3.96 (m, 1H), 3.93-3.86 (m, 1H), 3.38-3.28 (m, 2H), 3.26 (s, 3H), 3.11-2.99 (m, 1H), 2.05-1.95 (m, 1H), 1.19 (t, 3H, J = 7.1 Hz), 0.81 (d, 3H, J = 6.9 Hz).
449	 racemato, que contiene dos tipos de diastereómeros del Ejemplo No. 451.	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.50 (s, 1H), 8.57 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.65-4.59 (m, 1H), 4.47 (s, 2H), 4.30-4.24 (m, 1H), 4.01-3.96 (m, 1H), 3.33-3.24 (m, 2H), 3.11 (s, 3H), 1.92-1.86 (m, 1H), 1.70 (d, 3H, J = 6.4 Hz), 1.66-1.59 (m, 1H), 1.38 (d, 3H, J = 6.9 Hz), 1.33 (d, 3H, J = 6.9 Hz).
450	 racemato, que contiene dos tipos de diastereómeros del Ejemplo No. 452.	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.52 (s, 1H), 8.93 (s, 1H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.88-4.84 (m, 1H), 4.48 (s, 2H), 4.08-4.02 (m, 1H), 3.83 (t, 1H, J = 7.1 Hz), 3.44-3.37 (m, 2H), 3.23 (s, 3H), 3.04-2.96 (m, 1H), 1.84-1.73 (m, 2H), 1.41 (d, 3H, J = 6.9 Hz), 1.19 (t, 3H, J = 7.0 Hz).
451	 racemato, que contiene dos tipos de diastereómeros del Ejemplo No. 449.	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.50 (s, 1H), 8.95 (s, 1H), 7.42-7.38 (m, 2H), 7.21-7.16 (m, 2H), 4.91 (dd, 1H, J = 12.7, 5.8 Hz), 4.61-4.54 (m, 1H), 4.48 (s, 2H), 3.88 (d, 1H, J = 8.9 Hz), 3.50-3.39 (m, 2H), 3.24 (s, 3H), 1.91-1.85 (m, 1H), 1.69-1.61 (m, 1H), 1.39 (d, 3H, J = 6.9 Hz), 1.28 (d, 3H, J = 6.4 Hz), 1.26 (d, 3H, J = 6.4 Hz).
452	 racemato, que contiene dos tipos de diastereómeros del Ejemplo No. 450.	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.70 (s, 1H), 8.65 (s, 1H), 7.42-7.38 (m, 2H), 7.22-7.15 (m, 2H), 4.75-4.70 (m, 1H), 4.47 (s, 2H), 4.08-3.96 (m, 2H), 3.37-3.31 (m, 2H), 3.20 (s, 3H), 3.15-3.07 (m, 1H), 1.94-1.87 (m, 1H), 1.68-1.58 (m, 4H), 1.20 (t, 3H, J = 7.1 Hz).

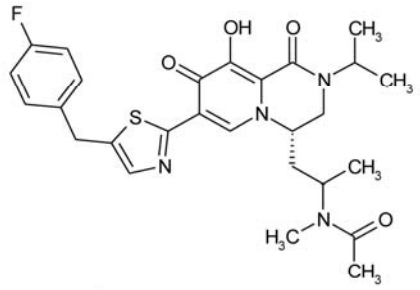
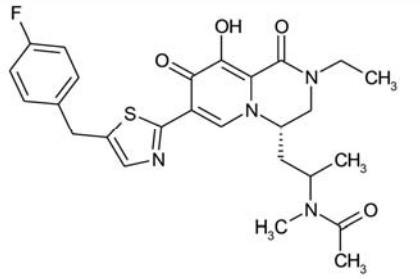
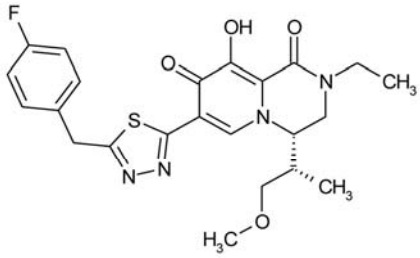
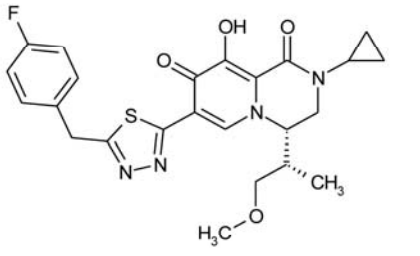
CUADRO 1-117

No.	fórmula estructural	sal	^{1}H-NMR
453		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.72 (br s, 1H), 8.81 (s, 1H), 7.45-7.39 (m, 2H), 7.23-7.15 (m, 2H), 4.95-4.88 (m, 1H), 4.78 (sep, 1H, J = 6.9 Hz), 4.47 (s, 2H), 3.81 (dd, 1H, J = 13.5, 3.4 Hz), 3.74-3.65 (m, 1H), 3.58-3.48 (m, 1H), 3.03 (s, 3H), 1.88-1.80 (m, 1H), 1.78-1.68 (m, 1H), 1.19 (d, 3H, J = 6.9 Hz), 1.16 (d, 3H, J = 6.9 Hz), 1.07 (d, 3H, J = 6.0 Hz).
454		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.67 (br s, 1H), 8.82 (s, 1H), 7.45-7.38 (m, 2H), 7.23-7.14 (m, 2H), 4.93-4.83 (m, 1H), 4.47 (s, 2H), 4.05 (dd, 1H, J = 13.5, 3.8 Hz), 3.71-3.42 (m, 4H), 3.05 (s, 3H), 1.95-1.86 (m, 1H), 1.82-1.71 (m, 1H), 1.16 (t, 3H, J = 7.1 Hz), 1.09 (d, 3H, J = 6.0 Hz).
455		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.82 (s, 1H), 7.43-7.40 (m, 2H), 7.21-7.16 (m, 2H), 4.88-4.83 (m, 1H), 4.46 (s, 2H), 3.98 (dd, 1H, J = 13.3, 3.6 Hz), 3.53 (dd, 1H, J = 13.3, 1.8 Hz), 3.52-3.46 (m, 1H), 3.02 (s, 3H), 2.98-2.93 (m, 1H), 1.86 (ddd, 1H, J = 14.3, 6.2, 2.6 Hz), 1.71 (ddd, 1H, J = 14.3, 8.8, 7.9 Hz), 1.08 (d, 3H, J = 6.0 Hz), 0.94-0.79 (m, 3H), 0.75-0.70 (m, 1H).
456	 diastereómero del Ejemplo No. 463	HCl	^{1}H-NMR (DMSO-d_6) δ: 8.66 (s, 0.7H), 8.50 (s, 0.3H), 7.70-7.64 (m, 1.0H), 7.37-7.30 (m, 2.0H), 7.19-7.11 (m, 2.0H), 4.70-4.62 (m, 0.3H), 4.59-4.51 (m, 0.7H), 4.44-4.34 (m, 0.7H), 4.20 (s, 2.0H), 4.08-3.99 (m, 1.0H), 3.80-3.70 (m, 0.3H), 3.69-3.47 (m, 3.0H), 2.80 (s, 2.1H), 2.69 (s, 0.9H), 2.12-1.86 (m, 4.3H), 1.83-1.73 (m, 0.7H), 1.22-1.12 (m, 3.0H), 1.05 (d, 0.9H, J = 6.4 Hz), 1.00 (d, 2.1H, J = 6.4 Hz).
457		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.80 (br s, 1H), 8.82 (s, 1H), 7.44-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.77 (sep, 1H, J = 6.9 Hz), 4.69-4.65 (m, 1H), 4.47 (s, 2H), 3.86 (d, 2H, J = 2.8 Hz), 3.37 (d, 2H, J = 5.2 Hz), 3.28 (s, 3H), 2.22-2.15 (m, 1H), 1.21 (d, 3H, J = 6.9 Hz), 1.18 (d, 3H, J = 6.9 Hz), 0.66 (d, 3H, J = 6.9 Hz).

CUADRO 1-118

No.	fórmula estructural	sal	^{1}H-NMR
458		HCl	^{1}H-NMR (DMSO-d_6) δ: 8.63 (s, 0.67H), 8.46 (s, 0.33H), 7.71-7.61 (m, 1H), 7.39-7.28 (m, 2H), 7.21-7.10 (m, 2H), 4.67-4.31 (m, 2H), 4.26-4.16 (m, 2H), 4.07-3.42 (br m, 2H), 3.03-2.56 (br m, 4H), 2.14-1.59 (m, 5H), 1.28-0.60 (m, 7H).
459	 diastereómero del Ejemplo No. 460	HCl	^{1}H-NMR (DMSO-d_6) δ: 9.18-8.08 (m, 1H), 7.49-7.10 (m, 4H), 5.28-3.81 (m, 6H), 3.07-2.45 (m, 4H), 2.36-1.64 (m, 5H), 1.38-0.32 (m, 7H).
460	 diastereómero del Ejemplo No. 459	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.72 (br s, 1H), 8.92-8.63 (m, 1H), 7.47-7.37 (m, 2H), 7.24-7.13 (m, 2H), 4.80-4.19 (m, 4H), 4.10-3.39 (m, 2H), 3.04-2.48 (m, 4H), 2.15-1.61 (m, 5H), 1.18-0.59 (m, 7H).
461	 diastereómero del Ejemplo No. 462	HCl	^{1}H-NMR (DMSO-d_6) δ: 8.63 (s, 1H), 7.68 (s, 1H), 7.37-7.29 (m, 2H), 7.19-7.10 (m, 2H), 4.90-4.65 (m, 2H), 4.61-4.45 (m, 1H), 4.20 (s, 2H), 3.89-3.55 (m, 2H), 2.81 (s, 3H), 2.00 (s, 3H), 1.95-1.76 (m, 2H), 1.29-1.11 (br m, 6H), 1.02 (d, 3H, J = 7.1 Hz).

CUADRO 1-119

No.	fórmula estructural	sal	^{1}H -NMR
462	 diastereómero del Ejemplo No. 461	HCl	^{1}H-NMR (DMSO-d_6) δ: 8.63 (s, 0.75H), 8.44 (s, 0.25H), 7.69-7.63 (m, 1H), 7.39-7.29 (m, 2H), 7.19-7.10 (m, 2H), 4.85-3.97 (m, 3H), 4.20 (s, 2H), 3.85-3.54 (m, 2H), 2.81 (s, 2.25H), 2.72 (s, 0.75H), 2.06-1.61 (m, 5H), 1.33-1.08 (m, 6H), 1.08-0.93 (m, 3H).
463	 diastereómero del Ejemplo No. 456	HCl	^{1}H-NMR (DMSO-d_6) δ: 12.58 (br s, 1.0H), 8.62 (s, 0.9H), 8.58 (s, 0.1H), 7.68 (s, 0.9H), 7.67 (s, 0.1H), 7.36-7.30 (m, 2.0H), 7.18-7.11 (m, 2.0H), 4.76-4.65 (m, 1.0H), 4.57-4.49 (m, 1.0H), 4.20 (s, 2.0H), 3.99-3.93 (m, 1.0H), 3.75-3.59 (m, 1.9H), 3.59-3.38 (m, 1.1H), 2.80 (s, 2.7H), 2.58 (s, 0.3H), 1.98 (s, 2.7H), 1.92-1.83 (m, 2.3H), 1.22-1.13 (m, 3.3H), 1.03 (d, 2.7H, J = 6.9 Hz).
464		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.72 (br s, 1H), 8.81 (s, 1H), 7.44-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.65-4.62 (m, 1H), 4.47 (s, 2H), 4.09 (dd, 1H, J = 13.7, 4.0 Hz), 3.82 (dd, 1H, J = 13.7, 0.8 Hz), 3.58 (dq, 1H, J = 13.3, 7.3 Hz), 3.53 (dq, 1H, J = 13.3, 7.3 Hz), 3.37 (dd, 1H, J = 9.7, 4.8 Hz), 3.32 (dd, 1H, J = 9.7, 6.4 Hz), 3.26 (s, 3H), 2.24-2.17 (m, 1H), 1.17 (t, 3H, J = 7.3 Hz), 0.72 (d, 3H, J = 6.9 Hz).
465		HCl	^{1}H-NMR (DMSO-d_6) δ: 12.71 (br s, 1H), 8.81 (s, 1H), 7.43-7.39 (m, 2H), 7.21-7.16 (m, 2H), 4.64-4.61 (m, 1H), 4.47 (s, 2H), 4.01 (dd, 1H, J = 13.7, 4.0 Hz), 3.72 (dd, 1H, J = 13.7, 1.2 Hz), 3.34-3.29 (m, 2H), 3.27 (s, 3H), 2.98-2.92 (m, 1H), 2.20-2.14 (m, 1H), 0.90-0.79 (m, 4H), 0.67 (d, 3H, J = 6.9 Hz).

EJEMPLO EXPERIMENTAL 1

Lo siguiente explica métodos de evaluación de la actividad inhibidora de la integrasa del VIH del compuesto de la presente invención.

(i) Construcción del sistema de expresión de genes recombinantes de la integrasa

Se insertó una secuencia génica de longitud total (No. de acceso: M19921) de integrasa del VIH–1 pNL4–3 en los sitios de enzimas de restricción *Nde* I y *Xho* I de plásmido pET21a(+) (fabricado por Novagen) para construir un vector de expresión de la integrasa pET21a–IN–tipo salvaje.

(ii) Producción y purificación de la proteína integrasa

Escherichia coli recombinante BL21(DE3) transformado con plásmido pET21a–IN–tipo salvaje obtenido en (i) se agitó en cultivo a 30 ºC en un medio líquido que contenía ampicilina. Una vez que el cultivo alcanzó la fase de crecimiento logarítmico, se añadió isopropil–β–D–tiogalactopiranósido para promover la expresión del gen de integrasa. El cultivo se continuó durante 5 h para promover la acumulación de la proteína integrasa. El *E. coli* recombinante se recolectó en aglomerados por separación centrífuga y se preservó a –80 ºC.

Este *Escherichia coli* se suspendió en tampón de lisis (50 mM de Tris–HCl (pH 7.6), 10 mM de $MgCl_2$, 5 mM de DTT) y se desestabilizó por

tratamientos repetidos de presurización y despresurización y la fracción insoluble se recolectó por centrifugación a 4 °C, 18,000 rpm durante 60 min. Esto se suspendió en tampón de lisis que contenía un inhibidor de la proteasa, se añadieron 1.25 mM de cloruro de sodio y 10 mM de CHAPS y la mezcla se agitó a 4 °C durante 30 min. La fracción hidrosoluble se recolectó por centrifugación a 4 °C, 9,000 rpm durante 30 min. La fracción obtenida se diluyó con un tampón en columna (50 mM de Tris–HCl (pH 7.6), 1 mM de DTT, 10% de glicerol, 10 mM de CHAPS) hasta 5 veces y la mezcla se aplicó a una columna de heparina (columna HiPrep 16/10 Heparina FF: fabricada por GE Healthcare Bio–Sciences). Usando un tampón en columna con NaCl 1 M, se eluyó una proteína con un gradiente de concentración de NaCl 0.1 M y se recolectó una fracción eluida que contenía una proteína integrasa. La fracción obtenida se diluyó 5 veces con un tampón en columna (50 mM de Tris–HCl (pH 7.6), 1 mM de DTT, 10% de Glicerol, 10 mM de CHAPS) y la mezcla se aplicó a una columna de intercambio catiónico (columna Mono–S: fabricada por GE Healthcare Bio–Sciences). Usando un tampón en columna que contenía NaCl 1 M, se eluyó una proteína con un gradiente de concentración de NaCl 0.1 M y se recolectó una fracción eluida que contenía una proteína integrasa. Las fracciones obtenidas de la proteína integrasa se recolectaron y preservaron a –80 ºC.

(iii) Preparación de una solución de ADN

El siguiente ADN sintetizado por FASMAC se disolvió en el tampón de TE (10 mM de Tris–ácido clorhídrico (pH 8.0), 1 mM EDTA) y se mezcló con ADN donante, ADN blanco y cada cadena complementaria (cadenas + y –) hasta 1 μM. La mezcla se calentó a 95 ºC durante 5 min, 80 ºC durante 10 min, 70 ºC durante 10 min, 60 ºC durante 10 min, 50 ºC durante 10 min y 40 ºC durante 10 min y se mantuvo a 25 ºC para dar un ADN bicatenario que se usó para el ensayo.

ADN donante (cadena + que tiene biotina unida a la terminal 5')

Cadena + donante: 5'–Biotina–ACC CTT TTA GTC AGT GTG GAA AAT CTC TAG CA–3' (SEQ ID NO: 1)

Cadena - donante: 5'–ACT GCT AGA GAT TTT CCA CAC TGA CTA AAA G–3' (SEQ ID NO: 2)

ADN blanco (cadenas +, – que ambas tienen digoxigenina unida a terminal 3')

Cadena + blanco: 5'–TGA CCA AGG GCT AAT TCA CT–Dig–3' (SEQ ID NO: 3)

Cadena – blanco: 5'–AGT GAA TTA GCC CTT GGT CA–Dig–3' (SEQ ID NO: 4)

(iv) Determinación de la actividad inhibidora de la enzima (integrasa del VIH)

El ADN donante se diluyó con tampón de TE hasta 20 nM, de lo cual se añadió 50 μl a cada cavidad de la placa negra revestida con estreptavidina (fabricada por PIAS Corporation) y se dejó adsorber a 37 °C durante 20 min. La placa se lavó con tampón de fosfato (Dulbecco's PBS, Sanko Junyaku Co., Ltd.) con 0.1% de Tween 20 y tampón de fosfato. A continuación, se añadieron una mezcla de reacción enzimática (70 μl), una sustancia de ensayo (10 μl) diluida con la mezcla de reacción enzimática y 0.75 μM de proteína integrasa (10 μl) a cada cavidad y la mezcla se hizo reaccionar a 37 °C durante 60 min.

Composición de la mezcla de reacción enzimática: 30 mM de MOPS (ácido 3–morfolinopropansulfónico), 5 mM de cloruro de magnesio, 3 mM de DTT (ditiotreitol), 0.1 mg/ml de BSA (albúmina de suero bovino), 5% de glicerol, 10% de DMSO (dimetilsulfóxido), 0.01% de Tween 20.

A continuación, se añadieron 25 nM de ADN blanco (10 μl) y la mezcla se hizo reaccionar a 37 °C durante 20 min y se lavó con tampón de fosfato que contenía 0.1% de Tween 20 para detener la reacción.

A continuación, se añadieron 100 mU/ml de solución de anticuerpos anti–digoxigenina rotulada con peroxidasa (Roche, 100 μl) y la mezcla se hizo reaccionar a 37 °C durante 60 min, seguido de lavado con tampón de fosfato que contenía 0.1% de Tween 20.

A continuación, se añadió solución de sustrato fluorescente de peroxidasa (fabricado por PIAS Corporation, 100 μl) y la mezcla se hizo reaccionar a temperatura ambiente durante 20 min a 30 min. Se añadió un líquido para neutralización de la reacción (fabricado por PIAS Corporation, 100 μL) para discontinuar la reacción y se midió la intensidad de la fluorescencia a una longitud de excitación de 325 nm/longitud de onda de fluorescencia de 420 nm.

La actividad inhibidora de la integrasa del VIH (IC_{50}) del compuesto de la presente invención se calculó a partir de la tasa de inhibición de acuerdo con la siguiente fórmula:

tasa de inhibición (%)=[1–(objeto–blanco)/(control–blanco)]×100

Objeto: intensidad de fluorescencia de la cavidad en presencia del compuesto de ensayo

Control: intensidad de fluorescencia de la cavidad en ausencia del compuesto de ensayo

Blanco: intensidad de fluorescencia de la cavidad en ausencia del compuesto de ensayo y la proteína integrasa

Los resultados se muestran en los siguientes cuadros.

CUADRO 2–1

Ejemplo No.	Actividad inhibidora IC_{50} (μM)
2	0.013
3	0.0085
4	0.01
5	0.0074
6	0.0056
7	0.013
8	0.0089
9	0.0091
10	0.0088
11	0.0064
12	0.0073
13	0.0064
14	0.01
15	0.013
16	0.02
17	0.0079
18	0.0082
19	0.0081
20	0.017

CUADRO 2–2

Ejemplo No.	Actividad inhibidora IC_{50} (μM)
21	0.0094
22	0.007
23	0.012
24	0.023
25	0.011
26	0.0076
27	0.01
28	0.015
29	0.01
30	0.009
31	0.0083
32	0.0077
33	0.0062
34	0.0082
35	0.0067
36	0.013
37	0.0063
38	0.012
39	0.01
40	0.013

CUADRO 2–3

Ejemplo No.	Actividad inhibidora IC_{50} (μM)
41	0.0072
42	0.0034
43	0.0046
44	0.0081
45	0.011
46	0.011
47	0.012
48	0.0069
49	0.0051
50	0.0064
51	0.0057
52	0.013
53	0.01
54	0.0075
55	0.021
56	0.01
57	0.011
58	0.017
59	0.012
60	0.017

CUADRO 2–4

Ejemplo No.	Actividad inhibidora IC_{50} (μM)
61	0.0066
62	0.0092
63	0.0083
64	0.0061
65	0.013
66	0.0064
67	0.0076
68	0.0098
69	0.013
70	0.0089
71	0.011
72	0.011
73	0.0077
74	0.0057
75	0.0091
76	0.0083
77	0.011
78	0.0089
79	0.0064
80	0.0098

CUADRO 2–5

Ejemplo No.	Actividad inhibidora IC_{50} (μM)
81	0.0075
82	0.0049
83	0.0071
84	0.011
85	0.0075
86	0.0095
87	0.0077
88	0.0087
89	0.008
90	0.0067
92	0.0087
93	0.0078
94	0.0088
95	0.0095
96	0.0067
97	0.0066
98	0.0075
99	0.0061
100	0.0081
101	0.0064

CUADRO 2–6

Ejemplo No.	Actividad inhibidora IC_{50} (μM)
102	0.0071
103	0.018
104	0.015
105	0.017
106	0.02
107	0.019
108	0.018
109	0.021
110	0.023
111	0.02
112	0.019
113	0.013
114	0.0081
115	0.012
116	0.0096
117	0.0094
118	0.013
119	0.011
120	0.015
121	0.016

CUADRO 2–7

Ejemplo No.	Actividad inhibidora IC_{50} (μM)
122	0.019
123	0.027
124	0.015
125	0.011
126	0.0073
127	0.014
128	0.019
129	0.012
130	0.013
131	0.013
132	0.0091
133	0.0074
134	0.016
135	0.012
136	0.011
137	0.0086
138	0.011
139	0.012
140	0.0058
141	0.008

CUADRO 2–8

Ejemplo No.	Actividad inhibidora IC_{50} (μM)
142	0.0064
143	0.0069
144	0.0077
145	0.0056
146	0.0059
147	0.0083
148	0.0098
149	0.0059
150	0.0061
151	0.0054
152	0.0059
153	0.0058
154	0.0073
155	0.01
156	0.0046
157	0.029
158	0.0054
159	0.0066
160	0.0061
161	0.0078

CUADRO 2–9

Ejemplo No.	Actividad inhibidora IC_{50} (μM)
162	0.0071
163	0.0077
164	0.0065
165	0.0074
166	0.012
167	0.01
168	0.0058
169	0.012
170	0.012
171	0.016
172	0.014
173	0.016
174	0.014
175	0.0095
176	0.0085
177	0.017
178	0.02
179	0.019
180	0.01
181	0.014

CUADRO 2–10

Ejemplo No.	Actividad inhibidora IC_{50} (μM)
182	0.0097
183	0.01
184	0.006
185	0.015
186	0.018
187	0.019
188	0.018
189	0.02
190	0.011
191	0.012
192	0.015
193	0.011
194	0.0082
195	0.0059
196	0.0067
197	0.014
198	0.0057
199	0.0084
200	0.0096
201	0.0095

CUADRO 2–11

Ejemplo No.	Actividad inhibidora $IC_{50}(\mu M)$
202	0.013
203	0.013
204	0.013
205	0.013
206	0.0059
207	0.024
208	0.012
209	0.012
210	0.023
211	0.016
212	0.014
213	0.015
214	0.016
217	0.0053
218	0.0065
219	0.015
220	0.0068
221	0.0084
222	0.0065
223	0.012

CUADRO 2–12

Ejemplo No.	Actividad inhibidora IC_{50} (μM)
224	0.0073
225	0.018
226	0.013
227	0.013
228	0.011
229	0.012
230	0.069
231	0.011
232	0.015
233	0.0064
234	0.018
235	0.016
236	0.013
237	0.013
238	0.018
239	0.016
240	0.052
241	0.014
242	0.013
243	0.0076

CUADRO 2–13

Ejemplo No.	Actividad inhibidora IC_{50} (μM)
244	0.074
245	0.0081
246	0.0084
247	0.01
248	0.014
249	0.012
250	0.017
251	0.011
252	0.0092
253	0.0077
254	0.0076
255	0.009
256	0.0082
257	0.0091
258	0.0093
259	0.009
260	0.012
261	0.011
262	0.01
263	0.009

CUADRO 2–14

Ejemplo No.	Actividad inhibidora IC_{50} (μM)
264	0.0085
265	0.0093
266	0.011
267	0.011
268	0.015
269	0.0094
270	0.0095
271	0.011
272	0.0089
273	0.014
274	0.012
275	0.014
276	0.016
277	0.012
278	0.0099
279	0.0063
280	0.016
281	0.016
282	0.015
283	0.018

CUADRO 2–15

Ejemplo No.	Actividad inhibidora IC_{50} (μM)
284	0.011
285	0.011
286	0.0078
287	0.008
288	0.0088
289	0.01
290	0.014
291	0.0087
292	0.0073
293	0.0096
294	0.011
295	0.012
296	0.019

CUADRO 2–16

Ejemplo No.	Actividad inhibidora IC_{50} (μM)
297	0.02
298	0.009
299	0.0098
300	0.009
301	0.008
302	0.0099
303	0.0058
304	0.0091
305	0.0095
306	0.01
307	0.011
308	0.013
309	0.0088
310	0.0099
311	0.0097
312	0.012
313	0.0097
314	0.0079
315	0.0088

CUADRO 2–17

Ejemplo No.	Actividad inhibidora IC_{50} (μM)
316	0.012
317	0.0098
318	0.0065
319	0.0058
320	0.0094
321	0.007
323	0.014

CUADRO 2–18

Ejemplo No.	actividad inhibidora IC_{50} (μM)
327	0.0059
328	0.0071
329	0.0061
330	0.0064
331	0.0093
332	0.012
333	0.0075
334	0.0091
335	0.0098
336	0.0072
337	0.017
338	0.0071
353	0.013
354	0.0080
355	0.0066
356	0.0089
357	0.0073

358	0.012
359	0.0048
360	0.011

CUADRO 2–19

Ejemplo No.	actividad inhibidora IC_{50} (μM)
361	0.015
362	0.010
363	0.0087
364	0.010
365	0.012
382	0.0087
383	0.0079
384	0.012
385	0.0082
386	0.015
387	0.011
388	0.0086
389	0.014

391	0.024
392	0.011
393	0.015
394	0.014
395	0.010
396	0.015
397	0.019

EJEMPLO EXPERIMENTAL 2

EVALUACIÓN DE LA ACTIVIDAD ANTIVIRAL

Se puede determinar el efecto del uso combinado del compuesto de la presente invención y los agentes anti–VIH existentes de la siguiente manera.

Por ejemplo, se evalúa el efecto del uso combinado de dos agentes de los inhibidores existentes de transcriptasa inversa nucleosídica (zidovudina, lamivudina, tenofovir), inhibidores de transcriptasa inversa no nucleosídica (efavirenz) o inhibidores de las proteasas (indinavir, nelfinavir) y la sustancia de ensayo A, y similares usando células CEM–SS infectadas con VIH–1 IIIB por medio del método XTT.

Además, se evalúa el efecto del uso combinado de tres agentes de la sustancia de ensayo A, zidovudina y lamivudina o la sustancia de ensayo

A, tenofovir y lamivudina, y similares.

Antes del ensayo del uso combinado, se miden IC_{50} y CC_{50} de cada medicamento solo. Se combinan 5 concentrados del medicamento A y 9 concentrados del medicamento B, determinados con base en estos resultados, para evaluar el efecto del uso combinado de dos agentes. Para el uso combinado de tres agentes, se mezclan un medicamento B altamente concentrado y un medicamento C; y el medicamento A y su concentración se combinan para evaluación.

Los resultados del ensayo de la sustancia de ensayo y el fármaco concomitante solo o en combinación se analizan sobre la base de los programas de Prichard y Shipman MacSynergy II versión 2.01 y Deltagraph versión 1.5d. Se esquematiza un diagrama tridimensional del % de inhibición en las concentraciones de cada medicamento combinado, obtenido de 3 ensayos, con 95% (o 68%, 99%) de límites de confianza y se evalúa el efecto del uso combinado con base en los valores numéricos de $\mu M^2\%$ calculados a partir de ello. Los criterios de evaluación se muestran a continuación.

Definición de interacción	$\mu M^2\%$
Fuerte acción sinérgica	>100
Ligera acción sinérgica	+51 – +100
Acción aditiva	+50 – –50
Ligera acción antagonista	–51 – –100
Fuerte acción antagonista	<–100

EJEMPLO EXPERIMENTAL 3

ENSAYO DE ESTABILIDAD METABÓLICA

Ensayo de estabilidad metabólica en microsomas hepáticos

Se suspenden microsomas hepáticos de especies humanas o animales (rata o mono) (fabricados por Xenotech LLC (Lenexa, KS, Estados Unidos), 20 mg de proteína/ml) (2.5 μl) y solución coenzimática generadora de NADPH (β–nicotinamida adenina dinucleótido fosfato: 5.2 mM, D–glucosa–6–fosfato: 13.2 mM de cloruro de magnesio: 13.2 mM de glucosa–6–fosfato deshidrogenasa: 1.8 U/ml) (50 μl) en 100 mM de tampón de fosfato de potasio (pH 7.4, 147.5 μl) y se mezclan con una sustancia de ensayo (2 μl) disuelta en acetonitrilo con 0.5% de DMSO. Después de incubar a 37 °C durante 0, 10 y 60 min, se añade acetonitrilo con ácido fórmico (concentración final 0.1%) y la mezcla se centrifuga. La sustancia de ensayo (forma no cambiada) en el sobrenadante se mide por cromatografía líquida de alto rendimiento/espectrometría de masa (LC/MS). La relación residual (%) se calcula a partir de los valores de medición obtenidos de acuerdo con la siguiente fórmula.

Relación residual (%) = cantidad de sustancia de ensayo después de la incubación (0, 10 ó 60 min)/cantidad de sustancia de ensayo con una incubación de 0 min x 100

Se prefiere como compuesto de la presente invención un

compuesto con una relación residual 60 min después no inferior al 40%, con mayor preferencia no inferior al 60%, con mayor preferencia no inferior al 80%.

El Ejemplo de Formulación se proporciona más abajo. Este ejemplo es meramente ilustrativo y no limita la invención.

EJEMPLO DE FORMULACIÓN

(a) compuesto del Ejemplo 1	10	g
(b) lactosa	50	g
(c) almidón de maíz	15	g
(d) carboximetilcelulosa sódica	44	g
(e) estearato de magnesio	1	g

Las cantidades totales de (a), (b) y (c) y 30 g de (d) se amasan con agua, se secan al vacío y se granulan. Los gránulos obtenidos se mezclan con 14 g de (d) y 1 g de (e) y se procesan en comprimidos con una máquina tableteadora para dar 1000 comprimidos con un contenido individual 10 mg de (a).

Aplicación Industrial

Los compuestos de la presente invención muestran una gran actividad inhibidora contra la integrasa del VIH.

En consecuencia, estos compuestos pueden ser medicamentos

efectivos, por ejemplo, para la profilaxis o el tratamiento de SIDA, como inhibidores de integrasa, agentes antivirales, agentes anti–VIH, y similares, que tienen una actividad inhibidora de la integrasa del VIH. Además, con el uso combinado con otros agentes anti–VIH tales como inhibidor de la proteasa, inhibidor de la transcriptasa inversa, y similares, pueden ser agentes anti–VIH más efectivos. Por otra parte, con una gran actividad inhibidora específica de la integrasa, pueden ser medicamentos seguros para el cuerpo humano con menor cantidad de efectos colaterales.

[Texto libre del listado de secuencias]

SEQ ID NO: 1: cadena+ donante para la medición de la actividad de la integrasa del VIH

SEQ ID NO: 2: cadena- donante para la medición de la actividad de la integrasa del VIH

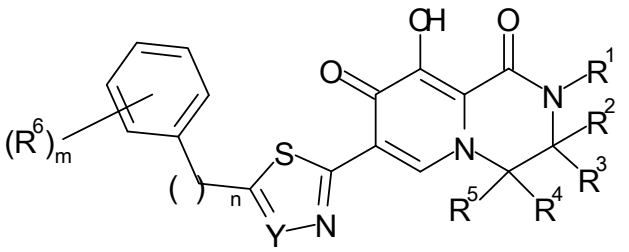
SEQ ID NO: 3: cadena+ blanco para la medición de la actividad de la integrasa del VIH

SEQ ID NO: 4: cadena- blanco para la medición de la actividad de la integrasa del VIH

NOVEDAD DE LA INVENCIÓN

REIVINDICACIONES

1.- Un compuesto representado por la siguiente fórmula [I] o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



[I]

en donde R^1 es (1) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de (i) un grupo cicloalquilo de C_{3-8}, y (ii) un grupo alcoxi de C_{1-6}, (2) un grupo cicloalquilo de C_{3-8}, o (3) un grupo heterocíclico monocíclico saturado que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, R^2, R^3, R^4 y R^5 son iguales o diferentes y cada uno es (1) un átomo de hidrógeno, (2) un grupo carboxilo, (3) $–CO–NR^aR^b$, en donde R^a y R^b son iguales o diferentes y cada uno es (i) un átomo de hidrógeno, (ii) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B, o (iii) un grupo cicloalquilo de C_{3-8}, o R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico

saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B, (4) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo A, o (5) un grupo ciano, o R^2 y R^3, o R^4 y R^5 forman opcionalmente, junto con el átomo de carbono al que están unidos, i) cicloalcano de C_{3-8}, o ii) un heteroanillo monocíclico saturado que contiene, además de átomos de carbono, 1 a 6 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, en donde R^2, R^3, R^4 y R^5 no son átomos de hidrógeno al mismo tiempo, R^6 es (1) un grupo alquilo de C_{1-6} opcionalmente sustituido con los 1 a 5 átomos de halógeno iguales o diferentes, (2) un grupo alcoxi de C_{1-6}, (3) un átomo de halógeno, o (4) un grupo cicloalquilo de C_{3-8}, Y es (1) CH, o (2) un átomo de nitrógeno, m es un número entero de 1 a 5 y cuando m es un número entero de 2 a 5, entonces cada R^6 puede ser igual o diferente, y n es un número entero de 1 a 3, grupo A: (a) $–CO–NR^{A1}R^{A2}$, en donde R^{A1} y R^{A2} son iguales o diferentes y cada uno es (i) un átomo de hidrógeno, (ii) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B, o (iii) un grupo cicloalquilo de C_{3-8}, o R^{A1} y R^{A2} forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de

átomos de carbono y un átomo de nitrógeno, 1 a 3 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados del siguiente grupo B, (b) un grupo hidroxilo, (c) un grupo alcoxi de C_{1-6}, (d) un grupo alcoxi de C_{1-6}–alcoxi de C_{1-6}, (e) un grupo ciano, (f) –$NR^{A3}R^{A4}$, en donde R^{A3} y R^{A4} son iguales o diferentes y cada uno es (i) un átomo de hidrógeno, (ii) un grupo alquilo de C_{1-6}, (iii) un grupo alquilcarbonilo de C_{1-6}, o (iv) un grupo alquilsulfonilo de C_{1-6}, o R^{A3} y R^{A4} forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 ó 2 grupos oxo, (g) un grupo carboxilo, (h) un grupo alquilsulfonilo de C_{1-6}, e (i) un grupo alquilcarbonilo de C_{1-6}; grupo B: (a) un grupo hidroxilo, (b) un grupo alcoxi de C_{1-6}, (c) un grupo alcoxi de C_{1-6}–alquilo de C_{1-6}, (d) un grupo cicloalquilo de C_{3-8}, y (e) un grupo oxo.

2.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque R^1 es un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de (i) un grupo cicloalquilo de C_{3-8}, y (ii) un grupo alcoxi de C_{1-6}, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

3.- El compuesto de conformidad con la reivindicación 2, caracterizado además porque R^1 es un grupo alquilo de C_{1-6}, o una sal

farmacéuticamente aceptable del mismo, o un solvato del mismo.

4.- El compuesto de conformidad con la reivindicación 2, caracterizado además porque R^1 es un grupo alquilo de $C_{1–6}$ sustituido con un grupo cicloalquilo de $C_{3–8}$, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

5.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque R^1 es un grupo cicloalquilo de $C_{3–8}$, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

6.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque uno de R^2, R^3, R^4 y R^5 es $–CO–NR^aR^b$ en donde R^a y R^b son iguales o diferentes y cada uno es (i) un átomo de hidrógeno, (ii) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o (iii) un grupo cicloalquilo de $C_{3–8}$, o R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

7.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque uno de R^2, R^3, R^4 y R^5 es un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes

seleccionados de grupo A, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

8.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque R^6 es un átomo de halógeno, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

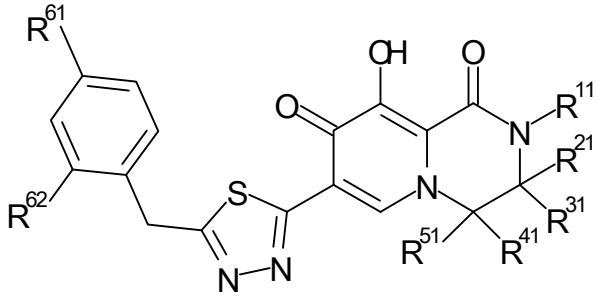
9.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque Y es CH, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

10.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque Y es un átomo de nitrógeno, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

11.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque m es 1 ó 2, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

12.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque n es 1, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

13.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la siguiente fórmula [I–1], o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



[I-1]

en donde R^{11} es (1) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de (i) un grupo cicloalquilo de $C_{3–8}$, y (ii) un grupo alcoxi de $C_{1–6}$, o (2) un grupo cicloalquilo de $C_{3–8}$, R^{21}, R^{31}, R^{41} y R^{51} son iguales o diferentes y cada uno es (1) un átomo de hidrógeno, (2) $–CO–NR^aR^b$ en donde R^a y R^b son iguales o diferentes y cada uno es (i) un átomo de hidrógeno, (ii) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o (iii) un grupo cicloalquilo de $C_{3–8}$, o R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o (3) un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A, en donde R^{21}, R^{31}, R^{41} y R^{51} no son átomos de hidrógeno al mismo tiempo, R^{61} es un átomo de halógeno, y R^{62} es un átomo de hidrógeno o un átomo de halógeno.

14.- El compuesto de conformidad con la reivindicación 13, caracterizado además porque R^{21} es un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A, y R^{31}, R^{41} y R^{51} son cada uno un átomo de hidrógeno, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

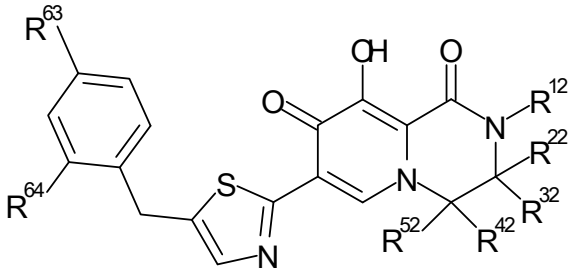
15.- El compuesto de conformidad con la reivindicación 13,

caracterizado además porque R^{21} es un grupo alquilo de $C_{1–6}$, y R^{31}, R^{41} y R^{51} son cada uno un átomo de hidrógeno, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

16.- El compuesto de conformidad con la reivindicación 13, caracterizado además porque R^{41} es un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A, y R^{21}, R^{31} y R^{51} son cada uno un átomo de hidrógeno, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

17.- El compuesto de conformidad con la reivindicación 13, caracterizado además porque R^{21} es un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A, R^{41} es un grupo alquilo de $C_{1–6}$, y R^{31} y R^{51} son cada uno un átomo de hidrógeno, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

18.- El compuesto de acuerdo con la reivindicación 1, caracterizado además porque está representado por la siguiente fórmula [I–2], o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



[I-2]

en donde R^{12} es un grupo alquilo de $C_{1–6}$ opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de (i) un grupo cicloalquilo de

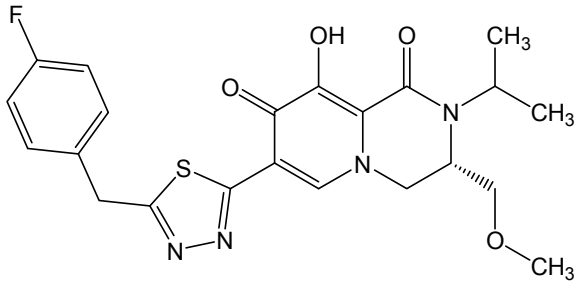
C_{3-8}, y (ii) un grupo alcoxi de C_{1-6}, R^{22}, R^{32}, R^{42} y R^{52} son iguales o diferentes y cada uno es (1) un átomo de hidrógeno, (2) –CO–NR^aR^b en donde R^a y R^b son iguales o diferentes y cada uno es (i) un átomo de hidrógeno, (ii) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o (iii) un grupo cicloalquilo de C_{3-8}, o R^a y R^b forman opcionalmente, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, o (3) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo A, en donde R^{22}, R^{32}, R^{42} y R^{52} no son átomos de hidrógeno al mismo tiempo, R^{63} es un átomo de halógeno, y R^{64} es un átomo de hidrógeno o un átomo de halógeno.

19.- El compuesto de conformidad con la reivindicación 18, caracterizado además porque R^{42} es –CO–NR^aR^b, en donde R^a y R^b forman, junto con el átomo de nitrógeno al que están unidos, un heteroanillo monocíclico saturado que opcionalmente contiene, además de átomos de carbono y un átomo de nitrógeno, 1 a 5 heteroátomos seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre y opcionalmente sustituido con 1 a 5 sustituyentes iguales o diferentes seleccionados de grupo B, R^{52} es un grupo alquilo de C_{1-6}, y R^{22} y R^{32} es un

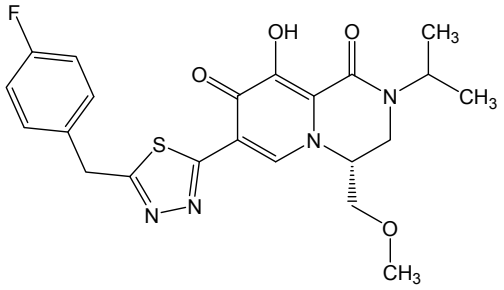
átomo de hidrógeno, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

20.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:

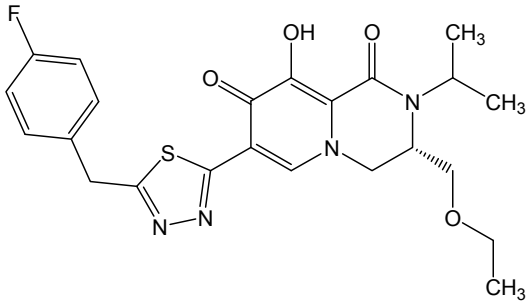
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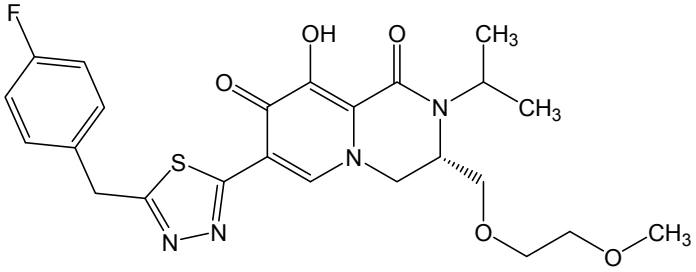
21.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



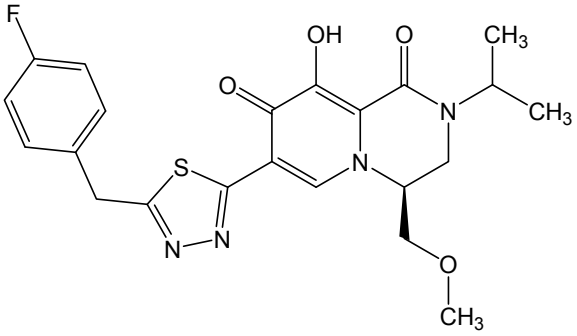
22.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



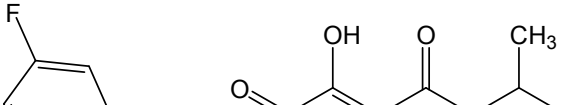
23.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



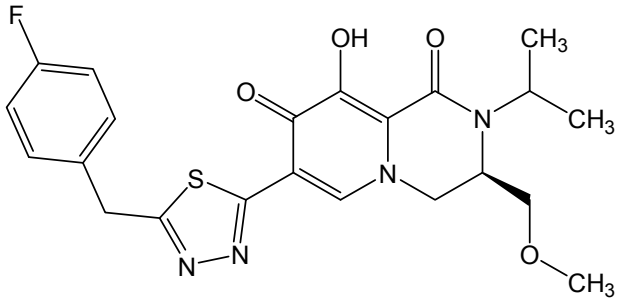
24.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



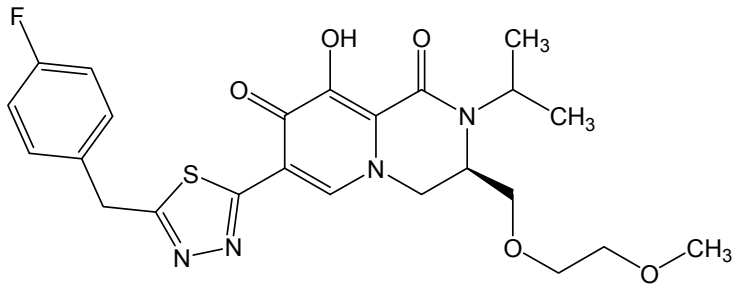
25.- El compuesto de conformidad con la reivindicación 1,



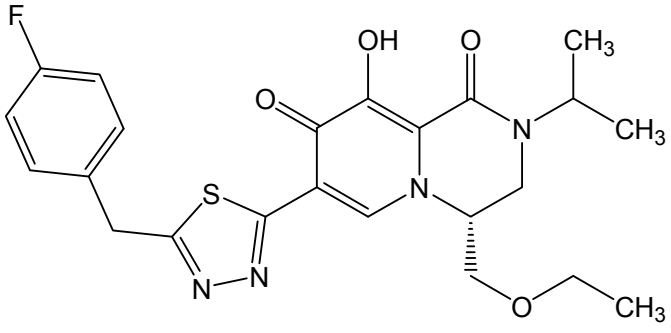
caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



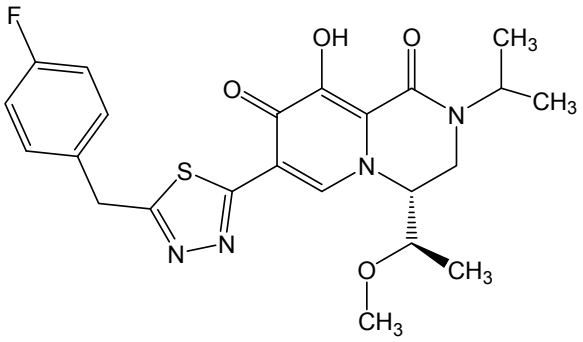
26.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



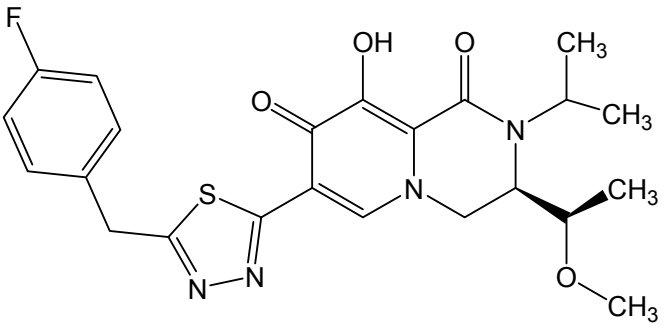
27.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



28.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



29.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo:



30.- Una composición farmacéutica que comprende el compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, y un portador farmacéuticamente aceptable.

31.- Un agente anti–VIH que comprende el compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, como un ingrediente activo.

32.- Un inhibidor de la integrasa del VIH que comprende el compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, como un ingrediente activo.

33.- Un agente anti–VIH que comprende el compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, en combinación con uno o más de otros tipos de sustancias activas anti–VIH.

34.- El uso del compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, para la producción de un agente anti–VIH.

35.- El uso del compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, para la producción de un inhibidor de la integrasa del VIH.

36.- Un método para la profilaxis o el tratamiento de una enfermedad infecciosa de VIH en un mamífero, el cual comprende la administración de una cantidad efectiva del compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, a dicho mamífero.

37.- El método de conformidad con la reivindicación 37, caracterizado además porque comprende adicionalmente la administración de una cantidad efectiva de uno o más de otros tipos de sustancias activas anti–VIH al mamífero.

38.- Un método para inhibir la integrasa del VIH en un mamífero, el cual comprende la administración de una cantidad efectiva del compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, a dicho mamífero.

39.- Una composición anti–VIH que comprende el compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, y un portador farmacéuticamente aceptable.

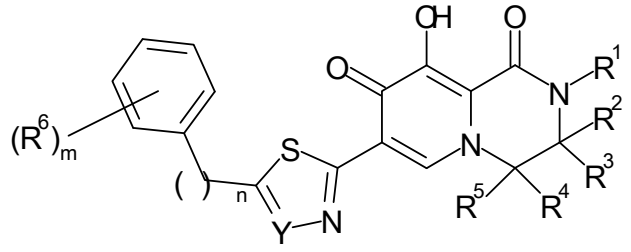
40.- Una composición farmacéutica para inhibir la integrasa del VIH, que comprende el compuesto de cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, y un portador farmacéuticamente aceptable.

41.- Un envase comercial que comprende la composición farmacéutica de la reivindicación 30 y un material escrito asociado con la misma, que establece que la composición farmacéutica se puede o se debe usar para tratar el VIH.

42.- Un kit que comprende la composición farmacéutica de la reivindicación 30 y un material escrito asociado con la misma, que establece que la composición farmacéutica se puede o se debe usar para tratar el VIH.

RESUMEN DE LA INVENCIÓN

Se provee un nuevo derivado de 1,3,4,8–tetrahidro–2H–pirido[1,2–a]pirazina o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo, que es útil como un agente anti–VIH; la presente invención provee un compuesto representado por la siguiente fórmula [I]



[I]

en donde cada símbolo es como se define en la especificación, o una sal farmacéuticamente aceptable del mismo, o un solvato del mismo.

LISTADO DE SECUENCIAS

<110> Solicitante: Japan Tobacco Inc.

<120> Título de la invención: 1,3,4,8–TETRAHIDRO–2H–PIRIDO[1,2–a]PIRAZINA Y SU USO COMO INHIBIDOR DE LA INTEGRASA DEL VIH

<130> Referencia de expediente: 091655

<150> Número de solicitud anterior: JP 2010-043567
<151> Fecha de presentación de solicitud anterior: 26–02–2010

<150> Número de solicitud anterior: US 61/339729
<151> Fecha de presentación de solicitud anterior: 09-03-2010

<160> Número de SEQ ID NOs: 4

<170> Software: PatentIn versión 3.5

<210> SEQ ID NO.: 1
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